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SOME ASPECTS OF TUBERCULOUS MENINGITIS AND THE POSSIBILITY OF ITS PREVENTION

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WITHOUT a doubt, tuberculous meningitis is the most fatal of all children's diseases. The morbidity and the mortality are identical. Not only is it a terribly malignant disease, but also it is a common one in childhood.

There are few other diseases against which we are as powerless as we are against tuberculous meningitis. In spite of all our therapeutic measures, it terminates inexorably in death. If anything is to be done to combat the disease, therefore, it must be done before it has developed—in other words, the meningitis must be prevented. Any hope of success in this respect will depend on a knowledge of the conditions under which the disease arises. I have taken it upon myself here to advance some views on this problem and to point out some progress in our knowledge made in recent times.

It is a fact well known to lung specialists that tuberculous meningitis appears only rarely, or not at all, in adults with pulmonary tuberculosis. It is, in fact, not a common complication with either tertiary or secondary organic tuberculosis. Among 166 autopsies carried out at our hospital on children who had died from tuberculous meningitis, only two presented postprimary organic tuberculosis. Evidently the meningitis develops most often before the tuberculosis has entered its secondary and tertiary stages.

It is not, however, the fact that the tuberculosis has passed into another, more advanced, stage, that diminishes the risk of meningitis.

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It is instead the fact that at such a more advanced stage the time at which the child was infected is farther in the past. In the necropsies, we usually find quite fresh tuberculous lesions, as is evident from Table I.

TABLE I

POSTMORTEM FINDINGS IN 166 CASES OF TUBERCULOUS MENINGITIS AT AUTOPSY AND X-RAY FINDINGS IN 39 CASES IN WHICH NO AUTOPSY WAS PERFORMED

	CALCIFIED		ENCAPSULATED		FRESH		TOTAL NUMBER
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	
Autopsy	9	5.4	20	12.0	137	82.6	166
X-ray	3	7.7	2	5.1	34	87.2	39

Among the 166 autopsied children, there was an old, calcified primary complex in only nine, while there were fresh anatomic changes

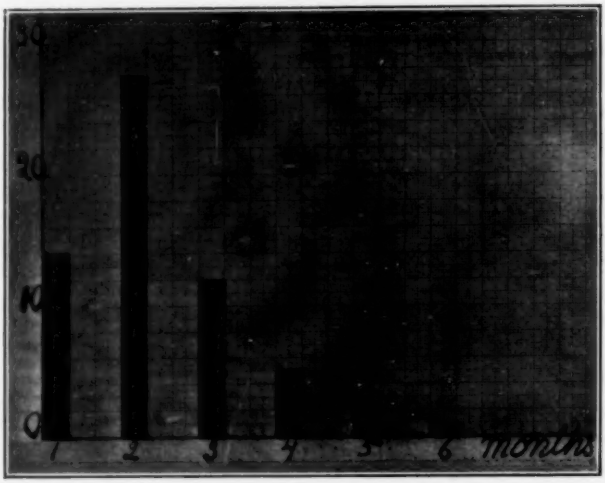

Chart 1.—The interval between manifestation of primary tuberculosis and meningitis (number of cases per month). After the sixth month there occurred only three additional cases.

in 137, i.e., 82.6 per cent. Among the thirty-nine children in whom no autopsy was made, but in whom the x-ray pictures revealed intrathoracic changes, these were calcified in only three cases, while there was fresh densification in thirty-four.

It is evident that, with only few exceptions, tuberculous meningitis develops as a complication to fresh, primary tuberculosis. As soon as encapsulation and calcification begin, the risk of meningitis is greatly diminished.

Primary tuberculosis becomes manifest at the same time as tuberculin sensitivity, i.e., from three to seven weeks after infection. Meningitis sets in while the primary tuberculosis is fresh. This period is not,

however, a definite one. A tuberculous lesion that is anatomically and roentgenologically fresh may actually be from six to twelve months old, while one that *looks* old may be of the same age. It is, in other words, not possible to judge from the aspect of the lesion how old it is. The question now is whether meningitis appears simultaneously with the development of primary tuberculosis or later, and in that case, when.

The appearance of meningitis in relation to that of primary tuberculosis may be ascertained if we know the date of the infection or of the first tuberculous manifestation. This is, however, very rarely the case. The observations of one single authority are not sufficiently informing on this question. Information must be obtained in many quarters. This has been done by the Hungarian physician, Orocz, and I have further contributed to this compilation with twenty additional cases. The total number of single observations which we now have at our disposal is about sixty. This is not, of course, an exaggeratedly large number, but, on the other hand, the results are markedly uniform (Chart 1).

The earliest symptoms of meningitis were observed in a few cases as early as a fortnight after the appearance of the allergy. It is not until the fourth week, however, that the cases accumulate, and two-thirds of all the cases of meningitis occurred in the course of the next month, with a maximum of frequency at six weeks. From the fourth month on, there were only sporadic cases. *It is evident that the child runs the greatest risk of getting meningitis between the fourth and the eighth weeks after the appearance of tuberculin sensitivity. Once three months have passed, the danger of meningitis is considerably less.*

These observations show that it is chiefly during the first three months after the development of primary tuberculosis that prophylactic measures are required. The question now is how the primary tuberculosis can be influenced so as to diminish the risk of meningitis during this critical period. One thing that could be done would be to prevent the occurrence of anything that might be likely to activate the tuberculous process still further and to place the child under as good hygienic care as possible.

The first condition of realizing this is that the primary tuberculosis should be diagnosed early. This is, however, not an easy task. The clinical symptoms of developing primary tuberculosis are very atypical, and the disease is seldom physically demonstrable. I should like to point out a symptom that very frequently accompanies the manifestation of primary tuberculosis. This is an entirely uncharacteristic fever, which in no way differs from that caused by commonplace infections. The only possible way of not overlooking primary tuberculosis is to make tuberculin tests in all acute febrile conditions, especially in such as are not clearly diagnosable. If the tuberculin test is positive, we must examine the lungs by x-ray. For some years back we have acted in

this manner in Gothenburg; this is probably the reason why we very frequently get children with quite fresh primary tuberculosis for treatment.

We prescribe sanatorium treatment. We keep the children in bed as long as the fever persists, as long as the blood sedimentation rate is accelerated. Then they are allowed a gradually increasing length of time during which they may be up and outdoors taking exercise. If the child is living under good social conditions and the family is capable of carrying out such measures, the child may be allowed to remain at home, but if not, he should be sent to a sanatorium during the critical period.

Many may regard this as far too rigorous a treatment in view of the common experience—numbers of children are found to have a healed primary complex without ever having received treatment at all. To this we can only reply that most cases of meningitis develop in children who have never been treated for their primary tuberculosis. It is indeed very rarely that meningitis develops during or after proper treatment for primary tuberculosis.

It is usually impossible to judge from the history of a meningitic child at what period he has passed through his primary tuberculosis. Which of the child's attacks of fever or "colds" reflected the disease is not known. But we do know this under one circumstance, viz., if the manifestation of the primary tuberculosis was accompanied by erythema nodosum. We know now that this syndrome is usually of tuberculous origin, appearing at the same time as tuberculin sensitivity, the manifestation of primary tuberculosis.

If we are told that a child with miningitis has had erythema nodosum, we know that his primary tuberculosis developed at the same time and may find out how or whether the child has been treated for it. At our hospital, we had such information about twenty-three children with tuberculous meningitis. Only three of these had had the treatment described. In four other cases, the symptoms of meningitis appeared so quickly after the onset of the primary tuberculosis that there was no time for regular treatment.

By way of comparison, I may mention that out of 428 children sent to our hospital and treated as I have described for erythema nodosum and primary tuberculosis, only three contracted meningitis. I may add that most children with erythema nodosum in Gothenburg are treated at home or at the hospital in the rigorous manner I have indicated here.

Knowledge of the time of predisposition to meningitis after the manifestation of primary tuberculosis may throw new light on the seasonal curve of meningitis. It is a well-known fact that tuberculous meningitis is most common during the spring months, as are most other tuberculous diseases. But in addition to this, our curve (Chart 2, lower curve)

shows an increase of meningitis cases in August. This is found in all statistics; in this respect, meningitis differs from other forms of tuberculosis. This August increase may seem extraordinary, but it can be explained by a corresponding peak in the seasonal curve of primary tuberculosis.

This curve (Chart 2, upper curve) shows a maximum of frequency from February to May and a minimum from July to September. Closer analysis of this seasonal curve reveals three separate peaks: one in October and November, one in January and February, and one in April and May. Probably these peaks are partly connected with the beginning of the school term in each case (the two first mentioned peaks) and with the increase in the number of sources of infection (pul-

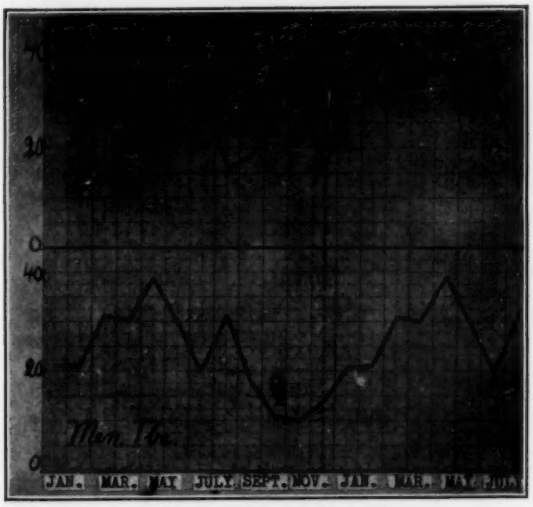

Chart 2.—The seasonal curves of primary tuberculosis (upper curve) and tuberculous meningitis (lower curve).

monary tuberculosis in adults) during spring (the last mentioned peak). Since the development of meningitis is intimately connected with the manifestation of primary tuberculosis and appears chiefly in the course of the first three months of this disease, corresponding peaks may be expected in the meningitis curve, though later than those of primary tuberculosis. Such is, in fact, the case. The smallest number of cases of meningitis occur in November. The first perceptible increase takes place in December and January, corresponding to the increase of the cases of primary tuberculosis in October and November. The frequency is then high all through the spring, but from March to May a fresh peak can be seen, corresponding to the peak in the primary tuberculosis curve in January and February. This is followed by a great diminu-

tion in the number of cases in June and July, interrupted by the previously mentioned third increase in August, corresponding to the April-May peak in the primary tuberculosis curve.

If the meningitis curve is placed on the primary tuberculosis curve so that January of the latter corresponds to March and May of the former, the two curves will be found to be almost parallel (Chart 3). If the proportion between primary tuberculosis and meningitis were equal under all circumstances, we might expect the August increase in meningitis to be at least as great as the March-April one, since the increase in primary tuberculosis is about the same in January and February as in April and May. Such is not the case, however. Apparently there is

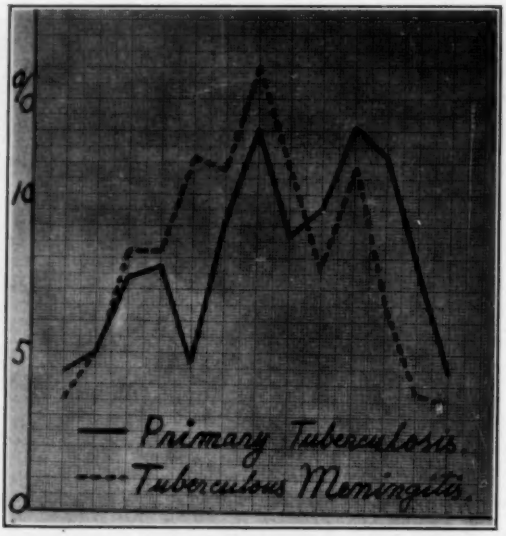

Chart 3.—The seasonal curves of primary tuberculosis (unbroken line) put upon that of tuberculous meningitis (broken line) in such manner that January of the former corresponds to April of the latter.

another factor increasing the tendency toward meningitis in the spring. Judging from this fact, it would seem that primary tuberculosis incurred during the late winter or early spring is more dangerous than one developing in the late spring or early summer. It would take us too far afield to inquire into the nature of this new factor, but it seems to me likely that it is the same as that which causes pulmonary tuberculosis to be more easily activated and manifested during the spring. From a prophylactic point of view, the lesson to be learned from this circumstance is that *uninfected children, in particular, must be protected against infection during the late winter and early spring, i.e., the first three or four months of the year.*

This is particularly important in the case of infants and small children since all children are not equally disposed to meningitis after a primary infection. *The younger the child, the greater the risk of meningitis.* This is plainly evident from the familiar age curve of meningitis (Chart 4, unbroken line). There is a considerable frequency of tuberculous meningitis during the first three years of life only, especially the first and second, after which the frequency drops very rapidly.

This cannot be due to any specially high frequency of primary infection in these first years since the very opposite is true; though the number of fresh infections is smallest in relation to later ages, we have here the greatest number of cases of meningitis. It follows that *the*

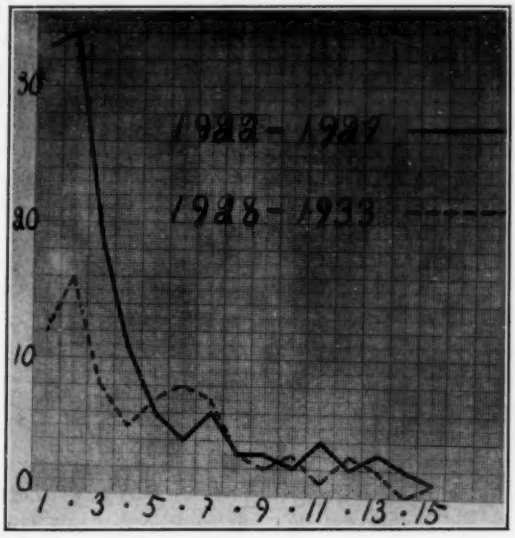

Chart 4.—The age curves of tuberculous meningitis at Gothenburg during the two six-year periods, 1922 to 1927 and 1928 to 1933.

danger of meningitis is infinitely greater if a child is infected during its first three years of life than later. Prophylaxis against meningitis should therefore be directed first and foremost against tuberculous infection in infants and small children.

That meningitis really can to a certain extent be prevented by rational antiinfection prophylaxis is shown by an age curve (Chart 4, broken-line curve) from the Gothenburg hospital for the last six years. In the course of this period, intensive dispensary work was carried on to prevent or forestall the dangers of tuberculous infection at an early age. A description of this work is beyond the scope of the present paper. A comparison of this curve with that of the immediately preceding six-year period (Chart 4, unbroken-line curve) at once reveals

the lack in the former curve of the striking peak for the first three years of life. On the whole, there are about the same number of cases of meningitis after the fifth year as during the six-year period, 1922 to 1927, while the number of cases during the first four years is markedly smaller than during the latter period. There is no doubt that this is a consequence of the above-mentioned prophylactic measures.

Now at the end of my paper, I should like to summarize what I have here advanced in the following way. It is evident that *tuberculous meningitis is a disease which can to a certain extent be prevented* with even the imperfect knowledge we have of the disease today. We must make every effort to utilize the means at our disposal and to apply them at the opportunities when they will do the greatest good. *Above all, we must try by every means to prevent tuberculous infection in infants and small children and give the best possible opportunities for recovery to those already freshly infected.* We cannot, at the present stage of our knowledge, prevent every case of tuberculous meningitis, but, while waiting for a better prophylaxis, we should, in my opinion, act as I have outlined here.

CHRONIC HYPOGLYCEMIA IN CHILDHOOD

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CASES of chronic hypoglycemia in adults are being reported in ever increasing numbers.[1-15] Very few cases of definite and persistent postabsorptive hypoglycemia in children have been reported. To our knowledge, only one case[16] has been described in the English literature and nine cases in the German literature.[17-21] During the past two years we had an opportunity to observe and study two children with chronic hypoglycemia. One of these (Case 1) presented a pathologic condition of the liver, e.g., fatty infiltration with absence of glycogen, which is, in our opinion, the first reported case of its kind, although the cases described by Björum and Debre (see footnote p. 304) may be of similar nature. In the light of these facts, a report of these patients with a general discussion and review of the literature especially as applying to children may be of value at this time.

In normal persons, the blood sugar level is maintained within narrow limits. According to present-day knowledge, the maintenance of the normal blood sugar level is accomplished by the constant rate of absorption of sugar from the alimentary canal, by the dual hepatic function of glycogenesis and glycogenolysis, and by insulin and adrenin, which influence liver activity, and the cellular process of glucose oxidation, utilization, and storage. In addition this process is sometimes regulated under abnormal or critical conditions by the nervous system and certain internal secretions.[22, 23]

Clinical data thus far obtained fail to reveal convincing evidence that significant lowering of blood sugar concentration can result from impairment of absorption of glucose from the alimentary tract, or from organic disease of the endocrine organs, or of the nervous system. On the other hand, there is a considerable number of cases in which chronic hypoglycemia was definitely due to disease of the liver[13-15, 17-21] and the pancreas.[1-12, 16] Hepatic hypoglycemia has occurred in many conditions in which there has been extensive replacement or destruction of liver tissue, such as in benign or malignant neoplasm, cirrhosis, toxic or infectious hepatitis, acute or subacute yellow atrophy, etc. Recently, von Gierke[18] and others[19-21] described a new clinical entity designated as "von Gierke's disease" or "hepatonephromegalia gly-

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kogenica,'' the main characteristic findings of which are chronic hypoglycemia and hepatic enlargement due to excessive accumulation and fixation of glycogen. The authors' case (Case 1), adds another type of hepatic hypoglycemia where glycogen is not produced and is apparently replaced by fatty infiltration. In all cases of hepatic hypoglycemia, the liver dysfunction, whether based on an organic lesion or functional disturbance, is either due to inadequate glycogenesis or glycogenolysis, or to impairment of both processes.

Pancreatic hypoglycemia is usually due to benign or malignant neoplasms of the pancreas, or to hypertrophy or hyperplasia of the islands of Langerhans. Hypoglycemia of lesser degree may be present in muscular dystrophies, starvation state, hypothyroidism, Addison's disease, during acute illnesses in children, and following severe muscular exertion.

In 1922, Wagner and Parnass[17] reported a case of a child, nine years of age, with hepatomegaly and hypoglycemia. The child displayed none of the usual symptoms of the hypoglycemia syndrome. The findings were those of a child with an enlarged liver, without associated splenomegaly or ascites. The child presented the appearance of dystrophia adiposogenitalis. It was the enlargement of the liver that led the authors to perform metabolic studies. They found that in the fasting state, with the methods then available, practically no sugar was demonstrable in the blood. Furthermore, there was in the urine no sugar but large amounts of ketone bodies. The latter disappeared after ingestion of sugar or starch. Other characteristics of the metabolism of the child were that a very sharp rise in the blood sugar took place with the intake of glucose, and this was accompanied by a marked glycosuria, both of which disappeared rapidly after a short time. After adrenalin injection no increase in the blood sugar concentration occurred. At first the authors felt that they were dealing with a condition in which the liver was no longer capable of forming glycogen from sugar. Several years later, in 1930, the authors by personal communication to von Creveld reported that their patient subsequently developed true diabetes mellitus. The starvation blood sugar had risen considerably and the liver had become much smaller.

Von Gierke[18] described the case of a girl, eight years of age, whose birth, neonatal, and early developmental history were apparently normal. A prominent abdomen was noted at two or three months of age. At three and one-half years an enlarged liver and spleen were palpable. No ascites was present, and the urine was negative. At five years of age she was observed in the hospital. At this time her appearance was infantile, and the liver was markedly enlarged. The spleen was not definitely palpable. She was subject to frequent upper respiratory infections and epistaxis. Her hemoglobin was 50 per

cent. She was observed for four more years during which time there was a tendency to further epistaxis and infections. The infantilism, low grade anemia, and enlargement of liver (lower edge of right lobe felt at the level of the umbilicus) persisted. Wassermann and tuberculin tests were negative. Except for a trace of albumin, examination of the urine including sugar and acetone bodies was negative. The child developed a severe influenzal infection at nine and one-half years of age and died after a few days of illness. Postmortem examination revealed a large liver weighing 2,000 gm. and large kidneys (the right weighing 120 gm. and the left 125 gm.). The enlargement was due to excessive accumulation of glycogen. Even on the sixth day after death, glycogen was still present in the liver, indicating probable absence of the glycogenolytic ferment.

The second case of von Gierke was a male child, four years and ten months old, who died as a result of a pneumonic infection. Fever, epistaxis, decline of nutrition, cyanosis, and dyspnea were the outstanding symptoms. The mother stated that the abdomen had been large since birth. The lower liver edge reached the level of the umbilicus. Postmortem examination showed a large liver weighing 1,860 gm., slightly enlarged heart, and spleen and kidneys of moderate size. In the liver, heart, and kidneys there was an unusual deposition of glycogen as in the first case. He assumed that here too the difficulty was due to absence of glycogen-splitting ferment. In these patients the hypoglycemia was obviously of hepatogenic origin. To this syndrome von Gierke applied the name "hepatonephromegalia glykogenica."

Von Creveld[19] reported the case of a boy, ten years old, who had been observed in various clinics practically since birth. The family history was irrelevant to the case. The birth history was normal. Shortly after birth an enlargement of the liver was noted. The enlargement was progressive, and on examination when he was one and one-half years old, the liver was found to be smooth, large and firm. An exploratory laparotomy confirmed the impression that the large mass was liver, but no excision of a portion of the organ was made. During the second year he suffered recurrent attacks of vomiting, which were interpreted as manifestations of cyclic vomiting. At six years of age, the boy seemed too small for his age and presented the appearance of dystrophia adiposogenitalis. The liver which was firm and smooth reached the level of the umbilicus. The spleen was not palpable, and ascites and polyuria were absent. The urine often showed acetone but was otherwise negative. Roentgenograms of the skeleton showed fewer than the normal number of centers of ossification. The sella turcica was negative. Thyroid and pituitary medication had no apparent effect. However, after three years, the centers of ossification were normal. The mental status was always normal.

Repeated blood sugar determinations over a period of years showed persistent hypoglycemia (from 30 to 46 mg. per 100 c.c.) unaccompanied by symptoms.

Ingestion of fructose caused a striking elevation of the blood sugar. A glucose tolerance test revealed a prolonged and biphasic curve which according to the author indicated a definite carbohydrate metabolic disturbance. A similar glucose tolerance test performed in the midday gave a more prolonged and elevated curve. Adrenalin injection caused only a slight rise of blood sugar from 40 to 56 mg. per 100 c.c. on one occasion, and another time a rise from 40 to 47 mg. per 100 c.c. In addition, respiratory quotient determinations following adrenalin injections showed a lowering of the quotient and an increased elimination of ketone bodies. During the height of ketonuria, vomiting occurred and was relieved by the ingestion of carbohydrate. This he interpreted as meaning failure of complete oxidation of fat due to inadequate glycogen mobilization. Respiratory quotient determinations following glucose administration revealed a normal response in a comparatively long period of time indicating a probable fixation of glucose as glycogen together with a slow burning of sugar. This was especially evident following fructose intake. Another confirmation of it was illustrated by the inorganic phosphorus in the urine which showed a slight decrease and late elimination as compared with the normal.

The child was observed for a period of three years by Creveld. No signs of diabetes mellitus appeared. Blood sugar concentration was still low but increased slightly during the last year. Postabsorptive urine showed acetone. Also the liver became smaller. Physical development improved. There was no enlargement of heart or kidneys by roentgenograms. A high carbohydrate diet was given with no recurrences of vomiting. Creveld's hypothetical explanation for the condition was that there was present a fetal abnormality which had persisted after birth. In premature infants there is a tendency to acetonemia and low blood sugar without symptoms. He believes that the trouble lies in the fermentative decomposition of glycogen in the liver and other tissue. The hypoglycemia in this case was definitely hepatogenic.

Schall[20] described the following three cases. One, a female child, eight and one-half years old, was subjected to exploratory operation, a piece of enlarged liver excised and found to contain an excess of glycogen. The other two patients were fourteen months and four years of age, respectively, both males, with markedly enlarged livers, in whom he assumed the same pathologic condition to exist. In all three cases, the family history was negative. Enlargement of the abdomen was noticed at birth in the first case, at four weeks in the

second, and during the first year in the third. In all three cases there was a definite retardation of physical development, but normal mental growth; a susceptibility to infection, an enlargement of the abdomen and liver with dilatation of the superficial abdominal veins but without caput medusae: a marked panniculus adiposus and a tendency to dyspnea and cyanosis. In the first two cases, the electrocardiogram was normal. The blood counts were normal. No glycogen was found in the blood. The Wassermann and tuberculin tests were negative. Urinalyses showed no sugar. In the first child, acetone was present in the urine during the postabsorptive period. Two or three hours after a meal, ketonuria disappeared. In the second, acetonuria occurred only in the febrile state. The third had acetonuria all the time. There was a characteristic hypoglycemia in all three cases, always under 50 mg. per 100 c.c. The lowest findings were 24, 25 and 19.5 mg. per 100 c.c. In spite of the marked hypoglycemia, no clinical signs such as are seen in cases of hyperinsulinism were present. The blood sugar curves after ingestion of glucose showed in all cases a departure from the normal. After a more or less sharp rise, there came a prolonged decline so that after three or four hours the curves did not return to the normal level. The same results were obtained with ingestion of other sugars. On successive administrations of glucose at hourly periods, a second and third superimposed curve and a marked prolongation of the curve occurred. An adrenalin test failed to produce a rise of the blood sugar. The respiratory quotient from two to four hours after intake of glucose rose to the value of about 1.

Observation over a period of from two to four years showed that the illness was not progressive. None of the patients developed diabetes mellitus.

Unshelm[21] reported two cases, in brothers, with enlarged livers since birth; they succumbed in the second year of life. A postmortem examination was made in the case of the second child. An excess of glycogen was found in the liver, brain, and to a lesser extent in the kidneys. The author felt that in this disease there was present some substance which protected the glycogen deposited in these organs against the factors which produced glycogenolysis. When he mixed normal liver and liver containing the excess of glycogen, no action was obtained. On the other hand, there occurred definite hydrolysis if the hyperglycogenic liver was minced. This indicated to Unshelm that the glycogen was capable of hydrolysis but that it could not be mobilized. (The ferment could not attack the glycogen in the intact cell.)

Wolfe, Hare, and Riggs[16] describe a case of hypoglycemia in a boy, 10 years old, in whom there were atypical convulsive seizures for

eighteen months, terminating in status epilepticus. The child was in the hospital during the last twelve days of his life. The blood sugar concentration varied from 32 mg. per cent to 54 mg. per cent. Necropsy revealed multiple adenomata of the pancreas. The symptoms were always predominantly of a neurologic nature, convulsions for eighteen months being practically the only symptoms.

In summary, of the ten reported cases of chronic persistent hypoglycemia in children, nine were of hepatic origin. The case of Parnass and Wagner[17] showed an interesting development in that the condition of hypoglycemia changed into one of diabetes mellitus. The other eight presented a characteristic clinical syndrome consisting of persistent hypoglycemia without any of the customary symptoms of hyperinsulinism; hepatomegaly, retardation of physical development; susceptibility to infection; and habitus of dystrophia adiposogenitalis. The tenth case was of pancreatic origin and had definite symptoms during life of hyperinsulinism, and on postmortem examination revealed an adenoma of the pancreas.

The two cases which we wish to report presented persistent postabsorptive hypoglycemia, one of probable hepatic origin as would be indicated from postmortem examination, and the other though etiologically still uncertain is in all probability due to a pancreatic lesion. The first case is of further interest because the pathologic changes in the liver, namely extensive fatty infiltration with hypoglycemia was not found in any of the other reported cases.*

The second case, in addition to the disturbance of carbohydrate metabolism, is of interest because of the remarkable neurologic features.

CASE REPORTS

CASE 1.—I. S. (Fig. 1), female, six months old, was admitted to the pediatric ward, Dec. 31, 1932, because of "poor appetite," "weakness," and "fainting (?) spells."

One sibling died at birth and another at two weeks of age, the cause in both cases being unknown. The family history was otherwise negative.

The child was born at term, weighing 7 pounds and 10 ounces. The birth was spontaneous and not difficult or prolonged. There was slight cyanosis for three days after birth, and the child nursed poorly. She gained slowly. At one month of age she had a generalized convulsion lasting two minutes. At five weeks the child was weaned. At three months of age the child had another generalized convulsion. In the following three months she had five or six attacks described as short

*In 1927, Björum[24] described four children in a family of eleven, all four of whom died within the first two years of life of an intercurrent infection. In each case, on postmortem examination an enormous fatty liver was revealed. Only transitory acute gastrointestinal symptoms were present. The possibility of phosphorus, arsenic, or alcohol poisoning was eliminated by the history. Unfortunately, blood sugar determinations were made only in the last of the four children. However, in this instance, the average was 80 mg. per 100 c.c. Debre et al.[25] reported a child with hepatic enlargement due to extensive fatty degeneration of the liver cells. The blood sugar content was not determined.

fainting spells. At six months she weighed only 12 pounds; she could not sit without support or hold her head up steadily. At this time, the patient was seen in the out-patient department. A large mass was found in the right side of the abdomen, and the patient was admitted for observation.

Examination on admission confirmed the findings of the out-patient department as far as size, weight, and development were concerned. The cry was lusty, and the child did not look acutely ill. The skin and mucous membranes appeared pale. There was no enlargement of the superficial lymph nodes. Ears, nose, and throat were negative. The anterior fontanel admitted four fingers. The head was 16¼ inches in circumference, the chest, 16 inches. There were no teeth. The heart and lungs were negative. The abdomen was large and prominent. The liver edge was felt three inches below the costal margin in the midline. The liver edge was sharp and the surface smooth. The spleen was not felt. There was a supernumerary digit attached to the proximal phalanx of the fifth finger of each hand. There was no clinical evidence of either tetany or rickets.

Fig. 1.—Case 1. I. S. at the time of admission.

LABORATORY DATA

Urine on admission showed a faint trace of albumin. All subsequent specimens showed nothing abnormal. On no occasion was sugar, acetone, or bile found.

Blood Count.—(Admission.) Hemoglobin, 71 per cent; red blood cells, 3,800,000; white blood cells, 10,600.

Differential: Polymorphonuclears, 29 per cent; lymphocytes, 64 per cent; monocytes, 3 per cent; eosinophils, 4 per cent.

Subsequent Blood Counts—

	HG.	*R.B.C.*	*W.B.C.*
7th day	70 per cent	3,880,000	11,860
12th day		4,000,000	18,000
15th day	60 per cent		
19th day	66 per cent	3,800,000	20,200
26th day	70 per cent	4,200,000	18,200

Blood.—Wassermann and Kahn reactions, negative.

Cerebrospinal Fluid.—Spinal fluid Wassermann and Kahn reactions were negative. Fluid, clear; cells, 6 per c.c. Pandy test, negative.

Stool Examination.—Normal appearance, yellow brown in color; bile present. No blood, pus, or parasites present.

Blood Chemical Analyses—

Jan. 9, 1933: BLOOD SERUM

CO_2	42.3	Volumes per cent
Cl	335.0	mg. per cent
NPN	44.0	mg. per cent
TN	1,110.0	mg. per cent
Total Protein (N × 6.25)	6.65	per cent
Refractive Index at 25° C.	1.3497	
Alb. N	556.0	mg. per cent
Glob. N	500.0	mg. per cent
A/G ratio	1.13	
Cholesterol	157.0	mg. per cent
Sugar	29.0	mg. per cent
Phosphorus [Inorganic]	4.1	mg. per cent
Total base	151.0	M. eq./L.

ACID BASE BALANCE

Total base	151 M. eq./L.
B Cl	95
B HCO_3	18
B Protein	16
Undetermined Acids	22

BLOOD SUGAR STUDIES (SEE TABLE I)

Jan. 9, 1933: Blood sugar one hour after feeding—87 mg. per cent.

Jan. 16, 1933 (11th day): Sugar tolerance test—

Fasting sugar	18 mg. per cent
Glucose ingested	15 grams
½ hr.	54 mg. per cent
1 hr.	112 mg. per cent
2 hr.	134 mg. per cent
3 hr.	119 mg. per cent

Jan. 17, 1933: Effect of adrenalin injection—

Fasting sugar	28 mg. per cent
Adrenalin injected	12 minims
10 min.	26 mg. per cent
20 min.	28 mg. per cent
40 min.	20 mg. per cent
60 min.	21 mg. per cent

Jan. 20, 1930: LEVULOSE TOLERANCE TEST

Fasting sugar	21 mg. per cent
Levulose ingested	15 grams
½ hr.	23 mg. per cent
1 hr.	18 mg. per cent
1½ hr.	17 mg. per cent
2½ hr.	25 mg. per cent
4 hr.	20 mg. per cent

Clinical Course.—The child's appetite remained poor. There was a slight irregular fever. Otherwise her condition remained unaltered. She was discharged as unimproved on the thirty-eighth day but was brought back on Mar. 4, 1933, six days after discharge, because of fever and cough. On the day of the second admission she had a severe convulsion. There were signs of pulmonary consolidation; these were confirmed by roentgenograms. The convulsions persisted, and the patient died several hours later. Blood sugar at this time was 8.3 mg. per cent, and spinal fluid sugar was 11.3 mg. per cent.

TABLE I

SUGAR TOLERANCE TESTS (I. S.)

	DEXTROSE 15 GM.	LEVULOSE 15 GM.
Fasting blood sugar	18 mg. per cent	21 mg. per cent
½ hr after ingestion	54 mg. per cent	23 mg. per cent
1 hr. after ingestion	112 mg. per cent	18 mg. per cent
1½ hr. after ingestion		17 mg. per cent
2 hr. after ingestion	134 mg. per cent	
2½ hr. after ingestion		25 mg. per cent
4 hr. after ingestion		20 mg. per cent

EFFECT OF ADRENALIN INJECTION (12 MINIMS)

	BLOOD SUGAR
Fasting	28 mg. per cent
10 min. after injection	26 mg. per cent
20 min. after injection	28 mg. per cent
40 min. after injection	20 mg. per cent
60 min. after injection	21 mg. per cent

POSTMORTEM EXAMINATION

I. S., aged nine months. Autopsy, March 5, 1933.

General Appearance.—The body was that of a thin, undernourished and poorly developed white female infant. The abdomen was distended. Each hand presented a supernumerary digit.

Peritoneal Cavity.—There was no free fluid or exudate present. The abdominal cavity was distorted by an enormously large liver filling about two-thirds of the abdomen and reaching to the pubis.

Gastrointestinal Tract.—There was nothing abnormal in the esophagus, stomach, small or large intestines. The mesenteric lymph nodes were considerably enlarged.

The liver was markedly enlarged, weighing 630 gm. The enlargement was diffuse and general in both lobes. It displaced the kidney and colon downward and to the left. The organ was pale, somewhat yellow in color, the surface smooth and glistening, and firm in consistency (Fig. 2). Upon section, it was pale yellow throughout. It was not greasy to the touch. There were no localized masses, nodules, or cysts. There was no evidence of biliary staining.

The gallbladder was filled with green bile which could be expressed through the normal biliary passages into the duodenum. The spleen appeared normal, weighing 16 gm. On section the organ was deep red, studded with prominent malpighian follicles measuring from ½ to 1 mm. in diameter. Pancreas weighed 7 gm. and appeared normal. There was no evidence of any nodules or masses; neither diffuse nor localized hyperplasia was present.

Cardiovascular System.—The heart was small, weighing 24 gm. The epicardium was wrinkled, but of normal thickness, and the coronary arteries were tortuous. The auricular and ventricular cavities were normal. The foramen ovale was not patent. The endocardium and valves were normal. The myocardium was pale and had a diffuse gray appearance. The pulmonary artery and aorta showed no abnormalities. The ductus arteriosus was patent by virtue of a fusiform passage.

Respiratory System.—The lungs were smooth, glistening, pink and crepitant. At the hilus of the left lung was a moderately firm, yellow noncrepitant, clearly demarcated portion of tissue measuring 2 × 2 × 2 cm. It was not surrounded by an inflammatory zone. A similar structure was found in the hilus of the right lung.

Fig. 2.

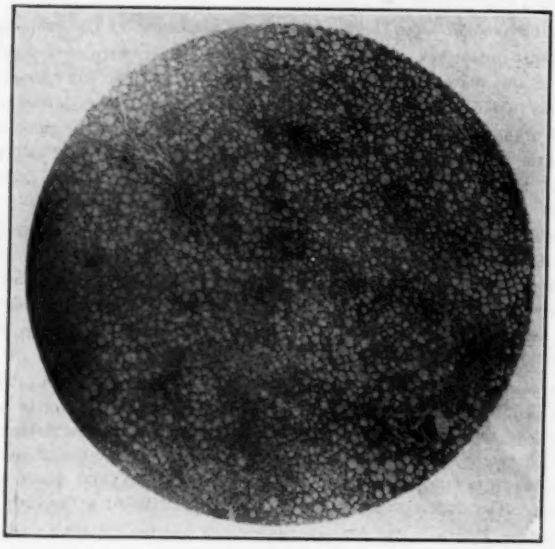

Fig. 3.

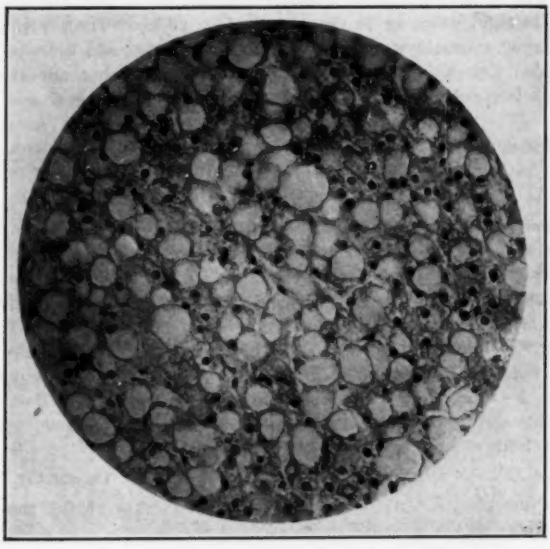

Fig. 4.

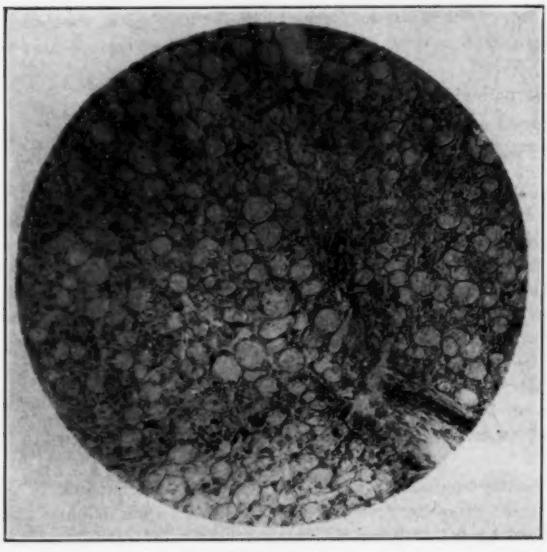

Fig. 5.

Genitourinary System.—The right kidney was displaced downward and inward by the liver. The lateral surface was considerably flattened. Both kidneys appeared small in size, the right weighing 18 gm. and the left, 20 gm. The capsules stripped with ease, exposing a smooth surface. On section, the cortex and medulla were well defined, but pale. Pelves and ureters were normal. Uterus, tubes, and ovaries were normal. The adrenal bodies appeared small and flat, weighing 2 and 2.3 gm., respectively.

The pituitary appeared normal.

Microscopic Examination

Liver.—Hematoxylin eosin stain. There was extensive fat replacement throughout the entire sections. Nowhere could one find normal liver cells (Fig. 3—low power). The vacuoles varied considerably in size, for the most part occupying the entire cytoplasm and displacing and flattening the nucleus at the periphery. In other cells only a small amount of granular cytoplasm remained (Fig. 4—high power magnification). Frozen sections stained with scarlet red, showed these globules stained bright red. Both large and small globules were seen in the cytoplasm of the liver cells (Fig. 5—stain of fat). Sections stained for glycogen with Best's carmine revealed no evidence of glycogen. The portal radicles appeared normal. There was no evidence of biliary staining.

Spleen.—The follicles were large, prominent and frequent in number.

Pancreas.—Numerous sections were made at various parts of the pancreas and nowhere were there any abnormalities found.

Heart.—Myocardial fibers appeared shrunken. Nuclei appeared closely crowded. No glycogen was demonstrable by Best's glycogen stain.

Lungs.—The yellow area described in the gross consisted of pulmonary alveoli which were separated by a moderate number of large vacuolated cells which had the appearance of fat. Within many of the alveoli in this region, were seen clasmatocytes containing numerous clear vacuoles. The lungs elsewhere appeared moderately congested.

Kidneys were normal.

Adrenals showed no definite changes.

Anatomical Finding.—1. Hepatomegaly due to fatty degeneration.
2. Lymphoid hyperplasia.

Case 2.—C. P., female infant, aged eight months, was admitted to the pediatric ward on Mar. 24, 1932. The chief complaint was difficulty in moving the left arm and leg noted one day prior to admission. The family history revealed nothing of importance. The child was said to have been premature, being the result of an eight-month pregnancy. The birth weight was 5½ pounds. There were no convulsions, cyanosis, icterus, or other neonatal abnormalities. She was artificially fed from birth, but the feeding history was normal and the diet entirely adequate, including all vitamins. Her development until the present illness was apparently satisfactory. The child held up her head at four months and sat up at six months. The first tooth erupted at six months. There was no story of any illness preceding the present admission.

One month before admission, when the patient was seven months of age, she began to have "fainting spells," lasting from one-half to one minute. These spells were characterized by flaccidity of the extremities, loss of consciousness, rolling of the eyes, and twitching of the eyelids. These episodes occurred every two or three days without apparent cause of warning. When they occurred, the patient usually had two or three attacks a day. After an attack the patient would become playful

and to all appearances quite normal. These attacks occurred at no special time of the day, and no definite relation to feeding time was noticed. On the day of admission Mar. 24, 1932, at 8:30 A.M. child began to cry fretfully and to refuse her feedings. At 1 P.M. of the same day, in a physician's office, it was noticed that the child could not move her left upper and lower limbs and that the face was drawn to the right when she cried. The temperature was 102° F. The doctor found no cause for the symptoms and advised hospitalization.

Examination on admission revealed a well-nourished and well-developed eight-month-old female infant who was irritable and cried a great deal but did not look acutely ill. The temperature was 103° F. by rectum. The head measured 17 inches in its greatest circumference. The chest was 18½ inches in circumference. Weight was 20 pounds, 7 ounces; height, 28 inches. The anterior fontanel admitted one and one-half fingers. The ears, eyes, and throat were negative. The heart, lungs, and abdomen revealed nothing abnormal. The skin was clear, and there was no glandular enlargement. No signs of rickets or tetany were present.

On neurologic examination it was found that the cranial nerves, except the right seventh, were apparently intact. There was an increased muscle tone in all ex-

Fig. 6. Case 2. C. P. at the age of nine months.

tremities; this was most striking on the left side. There was also a definite weakness of the left side. All deep reflexes were exaggerated. A bilateral positive Babinski reflex was present. Abdominal reflexes were not elicited. No Chvostek or Trousseau phenomena were present. The child's response to painful stimuli seemed normal.

LABORATORY DATA ON FIRST ADMISSION

Urinalysis.—A few clumps and scattered white blood cells, otherwise negative.

Blood Count.—Hemoglobin, 78 per cent; red blood cells, 4,200,000; white blood cells 10,200.

Differential: Polymorphonuclears, 58 per cent; lymphocytes, 40 per cent, monocytes, 2 per cent.

Cerebrospinal Fluid.—Normal pressure; four cells, all lymphocytes. Pandy test was negative. Sugar, 20 mg. per cent; calcium, 5.2 mg. per cent; phosphorus, 1.9 mg. per cent. Wassermann and Kahn reactions negative.

Tuberculin.—Negative.

Blood Chemistry.—Calcium, 11.0 mg. per cent; blood inorganic phosphorus 5.4 mg. per cent.

Fasting blood sugar, 45 mg. per cent.

X-ray of extremities showed normal number of centers of ossification. No evidence of rickets.

Clinical Course.—The weakness of the left side disappeared on the second day. The temperature dropped to normal and the child appeared improved, and was taken home, on the insistence of the mother, on the fifth day after admission before further metabolic studies could be made. Two days after discharge the child had a recurrence of extreme irritability. The mother noticed a weakness of the right side of the body and brought the child back for readmission to the hospital.

Examination on the Second Admission

The weakness of the right side reported by the mother had disappeared, but there was a residual slight hypertonicity of all four extremities with a transient positive Babinski reflex on the left side. The child was irritable but did not look acutely ill. It was noticed at this time that she was unable to sit steadily. Attention to surroundings was too flighty even for an infant of this age, and the question of the presence of mental deficiency in this child arose. The patient remained in the hospital for one month during which time studies were made in an attempt to determine the underlying cause of the hypoglycemia.

Blood Sugar Studies (See Table II)

Glucose tolerance tests*—

Apr. 4, 1933: Fasting blood sugar 65 mg. per 100 c.c. of blood.
25 gm. of glucose ingested.
Blood sugar one hour later—175 mg. per cent.
Two and one-half hours later—162 mg. per cent.

Apr. 11, 1933: Fasting blood sugar, 45 mg. per 100 c.c. of blood.
25 gm. of glucose ingested.
Blood sugar one hour later—69 mg. per cent.
Two and one-half hours later—46 mg. per cent.
Four hours later—31 mg. per cent.

Table II

Sugar Tolerance Tests

DATE	NATURE OF SUGAR	AMOUNT IN GRAMS	BLOOD SUGAR IN MG. PER CENT						
				TIME AFTER INGESTION					
			F. B. S.	½ HR.	1 HR.	1½ HR.	2 HR.	2½ HR.	4 HR.
4/ 4/33	Dextrose	25	65		175			162	
4/11/33	Dextrose	25	45		69			46	31 mg.
4/14/33	Dextrose	25	57		86				
4/21/33	Dextrose	25	57	113				102	
8/23/33	Dextrose	50	81	186		147		93	
9/12/33	Dextrose	50	58	188		271		215	
1/29/34	Dextrose	50	79	131				112	
9/13/33	Levulose†	45	55	89		140	155		
9/16/33	Levulose†	25	56	78		82	87		
9/ /	Galactose†	20	61	75		75	78		
9/23/33	Galactose†	30	52	78		71	56		

†Urines negative for reducing substances.

*The apparent significant variations obtained in the different sugar tolerance tests may be due to marked fluctuations, not only in the endogenous production of insulin but in the other physiological processes concerned in carbohydrate metabolism.

Apr. 14, 1933: Fasting blood sugar—57 mg. per cent.
25 gm. of glucose ingested.
Blood sugar one hour later—86 mg. per cent.

Apr. 21, 1933: Fasting blood sugar—57 mg. per cent.
25 gm. of glucose ingested.
Blood sugar, ½ hour later—113 mg. per cent.
Two and one-half hours later—102 mg. per cent.

Epinephrine Test (Table III)—

Apr. 13, 1933: Fasting blood sugar—44 mg. per 100 c.c. of blood.
10 minims of adrenalin administered.
Blood sugar—10 min. later—66 mg. per 100 c.c.
25 min. after administration—107 mg. per 100 c.c.
40 min. after administration—134 mg. per 100 c.c.
55 min. after administration—130 mg. per 100 c.c.
70 min. after administration—134 mg. per 100 c.c.

Postabsorptive Blood Sugar—

In addition to the fasting blood sugar determinations, three additional postabsorptive blood sugar examinations were made. The blood was obtained in the afternoon.

Blood sugar—38 mg. per 100 c.c.
Blood sugar—36 mg. per 100 c.c.
Blood sugar—33 mg. per 100 c.c.

Urines—

Frequent urinalyses including specimens obtained during the sugar tolerance tests showed no sugar, acetone, or diacetic acid.

TABLE III

EFFECT OF ADRENALIN INJECTIONS—10 MINIMS

	BLOOD SUGAR
Fasting	44 mg. per cent
10 min. after administration	66 mg. per cent
25 min. after administration	107 mg. per cent
40 min. after administration	134 mg. per cent
55 min. after administration	130 mg. per cent
70 min. after administration	134 mg. per cent

Clinical Course.—The child was very irritable most of the time and appeared listless, inattentive, and pale. Frequent high carbohydrate feedings seemed to allay the irritability and listlessness, and periods of cheerfulness and alertness became more frequent. The child appeared to several observers to be mentally defective. A careful examination to determine the neurologic and mental status of the child including encephalography and the Gesell test was undertaken on the thirtieth day in the hospital, when the child was nine months of age.

Neurologic examination revealed slight increase in muscle tone in all extremities. The left positive Babinski reflex was still present. There was no obvious palsy or paresis. Deep reflexes were hyperactive, abdominal reflexes all present at this time. There were no cranial nerve palsies. Fundi were negative. No sensory loss was demonstrable. Child could not sit long without support and tended to fall to the left. She seemed definitely ataxic in reaching for objects and the question of cerebellar lesion arose.

The Gesell test showed failure of performance above the six-month level. Visual and auditory attention was poor and excessively flighty and motor control, defective. The latter was thought to be due to the ataxia. Adaptive behavior was similarly at about the six-month level.

The encephalogram was interpreted by radiologists as indicating dilatation of the lateral and third ventricles, especially in the third (Figs. 7 and 8).

The patient was discharged on the thirty-sixth day at the age of nine and one-half months.

Fasting blood sugar two days before discharge was 38 mg. per cent, and a casual blood sugar test at 1:50 P.M. on the same day was 36 mg. per cent.

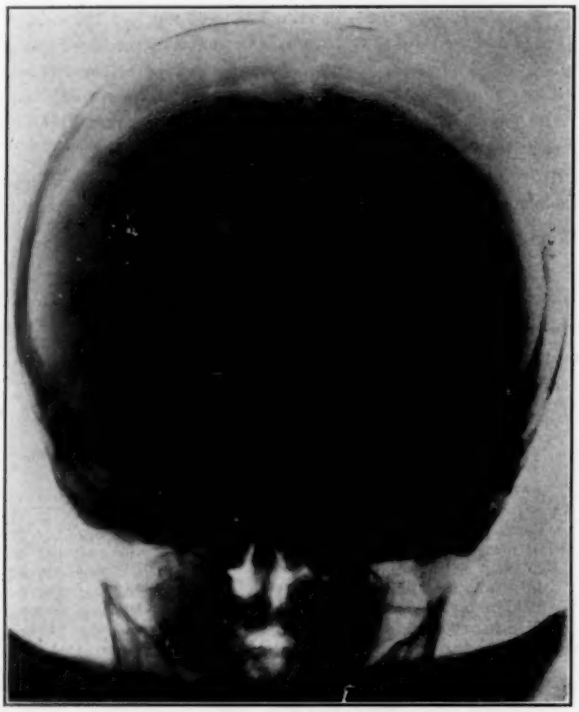

Fig. 7.

Further observation by the family physician and our out-patient department showed that the child on a regime of frequent carbohydrate feedings had fewer attacks of fainting spells. On three occasions, at eleven months, thirteen months, and fourteen months of age, however, the patient had transient hemiplegias of one or the other side. At eleven months she sat up steadily alone; at thirteen months she stood with support; and at eighteen months she walked alone but unsteadily. Even at this time (eighteen months of age) the patient seemed very restless and hyperkinetic. Attention still was poor. The patient, when subjected again to the Gesell test, failed to perform beyond the twelve-month level. Except for some unsteadiness, ataxic groping with hands and somewhat unsteady gait, and increased

muscle tone and bilateral Babinski, there were no abnormal neurologic findings. At eighteen months the patient appeared obese. The weight was 32 pounds, 12 ounces, the average for weight and height being 25 pounds.

After this, she had spells of restlessness and irritability but no fainting spells or recurrences of the hemiplegia.

Aug. 23, 1933: (Patient, twenty-six mo. old.) Blood sugar—81 mg. per cent (nonfasting).

Glucose— 50 gm.
½ hr.—186 mg.
1½ hr.—147 mg.
2½ hr.— 93 mg.

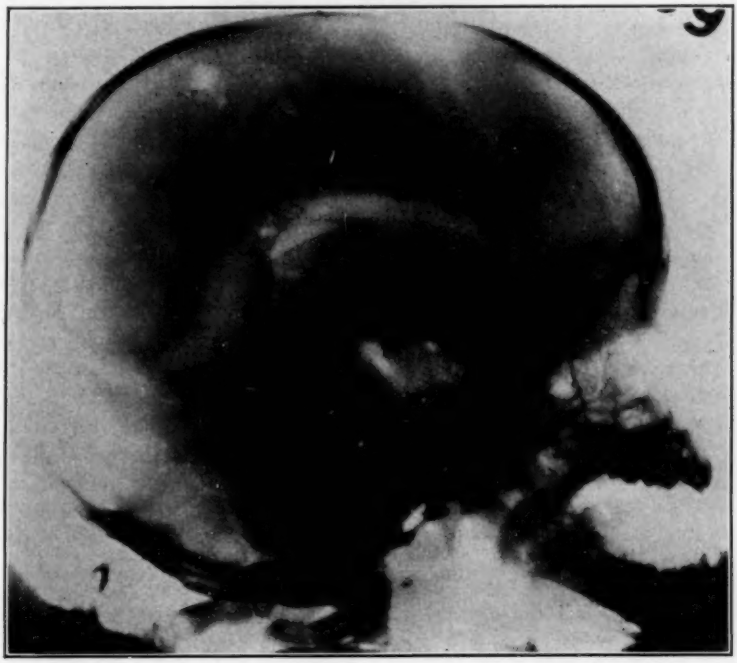

Fig. 8.

Urine voided two hours after beginning of the test showed 0.5 per cent sugar or 0.6 gm. of glucose.

She was readmitted on Sept. 8, 1933. The status was unchanged from the previous examination.

LABORATORY DATA ON THIRD ADMISSION

Sept. 12, 1933: Glucose tolerance test—
Fasting blood sugar—58 mg. per cent.
50 gm. of glucose ingested.
Blood sugar ½ hr. later—188 mg. per cent.
Blood sugar 1½ hr. later—271 mg. per cent.
Blood sugar 2½ hr. later—215 mg. per cent.

Levulose tolerance test—	September 13	September 16
Fasting blood sugar	55 mg. per cent	56 mg. per cent
Levulose ingested	45 gm.	25 gm.
Blood sugar ½ hr. later	89 mg. per cent	78 mg. per cent
Blood sugar 1½ hr. later	140 mg. per cent	82 mg. per cent
Blood sugar 2 hr. later	155 mg. per cent	87 mg. per cent

A faint trace of reducing substance was found in the two specimens collected on Sept. 13, 1933.

Fig. 9.—Case 2. C. P. at the age of two years.

Galactose tolerance test—	Sept. 23, 1933	Sept. 25, 1933
Fasting blood sugar	61 mg. per cent	52 mg. per cent
Galactose	20 gm. ingested	30 gm. ingested
Blood sugar ½ hr. later	75 mg. per cent	78 mg. per cent
Blood sugar 1½ hr. later	75 mg. per cent	71 mg. per cent
Blood sugar 2 hr. later	78 mg. per cent	56 mg. per cent

An exploratory laparotomy revealed no palpable neoplasm. The surgeon did not resect any portion of the pancreas.

DISCUSSION

To our knowledge, chronic hypoglycemia due to extensive fatty infiltration of the liver with complete absence of glycogen, as found in Case 1, is the first reported case of its kind.*

*After the completion of our paper, our attention was called by Dr. Wilder to the report of Judd et al.[28] citing two cases of hypoglycemia in adults associated with fatty changes in the liver. One patient who was diabetic was being treated with insulin. A biopsy showed "fatty metamorphosis of the liver." The other was an unexplained hypoglycemia producing symptoms characteristic of hyperinsulinism. A section of a piece of liver showed an unusual occurrence of droplets of fat. The pancreas appeared normal on inspection and palpation. The possible existence of a pathologic condition in this organ in the latter case must still be entertained.

This condition was apparently not due to an acute poisoning, such as phosphorus poisoning, etc. The age of the child, the intake of only its prescribed diet and the absence of acute gastrointestinal symptoms and other evidences of acute toxicity eliminate this possibility.

Several interesting features are presented by this case. The unexplained early death of the other two children leads one to the belief that they probably had a similar condition, which may, therefore, be familial. It was the incidental finding of a mass in the abdomen which was interpreted as enlarged liver that led to the special study which revealed the nature of the condition. The data obtained by our investigation indicates that the hypoglycemia was due to the failure of the liver to maintain a normal blood sugar level due to inadequacy or absence of glycogenesis and glycogenolysis. That the liver plays a most important rôle in this physiologic process is now unquestioned. The comparatively marked elevation of the blood sugar following the intake of glucose with a relatively abnormal prolongation of the blood sugar curve may be due to impairment of function of glycogenesis. Similar curves were obtained by Mann and his coworkers[27] in their dehepatized dogs. Also the failure of an injection of an adequate dose of adrenalin to produce an elevation of blood sugar is another proof of the existence of a significant degree of either aglycogenesis or aglycogenolysis in the liver or of the presence of dysfunction of both processes. That this response was not due to an inability to utilize and oxidize the supplied glucose was proved by the presence of a continuously markedly subnormal postabsorptive blood sugar and the absence of glycosuria and symptoms of diabetes mellitus. That the disturbance was hepatogenic was further substantiated by the postmortem examination, which revealed a liver extensively infiltrated with fatty material.*

The chemical and pathologic evidences indicate that we are probably dealing with a selective hepatic functional disturbance of carbohydrate metabolism, e.g., aglycogenesis, which in turn led to aglycogenolysis and fatty infiltration. There was no disturbance of carbohydrate combustion as evinced by absence of symptoms of diabetes mellitus, of glycosuria, of postabsorptive hyperglycemia, and of ketone bodies. That the rôle of the liver in the metabolism of proteins was unaltered was shown by the normal blood chemical findings showing no increase of nonprotein nitrogen. There was no gross lipemia or increase of cholesterol in the blood. Bile production and excretion were normal, as presumed by the presence of sufficient amounts of bile in the gallbladder and feces, and by the absence of bile in the urine. Blood plasma volume was normal, as indicated by the normal refractive index. Hepatic function, therefore, as far as

*Chemical studies of the nature of the fatty material in the liver are being undertaken and will be reported.

all other metabolic processes were concerned, was apparently normal. The absence of glycogen in the liver was probably due to the hepatic inability to transform glucose into glycogen.

The probabilities are that in this child there was a selective liver dysfunction. The primary disturbance was marked impairment or absence of hepatic glycogenesis resulting in failure of deposition of glycogen in the liver and consequently no glycogenolysis. Furthermore, this hepatic inability to transform in a normal manner the glucose in the portal circulation might have resulted in its conversion into fat. Except for this possible explanation, we are at a loss to give a cause for the disturbance.

The second case presented a persistent postabsorptive hypoglycemia which manifested itself in characteristic symptoms of varying intensity. Ingestion of food ameliorated the symptoms. The sugar tolerance tests revealed various types of responses, e.g., a normal blood sugar curve, a very low rise and on two occasions an unusual elevation and prolongation in the curve. These fluctuations indicate variability in the physiologic state of the organs and tissues participating in carbohydrate metabolism. These occur normally, but are usually more evident in pathologic conditions. This variability of the blood sugar concentration following intake of glucose was obtained in cases of hyperinsulinism.[1-12] Intake of levulose and galactose gave normal curves and no significant glycosuria. Ingestion of adrenalin produced the usual hyperglycemia.

The data obtained indicate that the liver was not responsible for the condition in this case. The functions of glycogenesis and glycogenolysis seemed intact. The relatively subnormal blood sugar response to the intake of glucose indicates a rapid oxidation and utilization of dextrose, possibly due to hyperinsulinism. The absence of an enlarged liver and the adrenalin hyperglycemia probably speaks against hepatic hyperglycogenesis, because all the reported cases of the latter condition had significant hepatomegaly and failed to respond to epinephrine administration.

The absence of any evidence of myopathies or scleroderma in this case eliminates these as the basis of the subnormal blood sugar.

Up to this time as far as we know, no one has observed a definite case of persistent and striking hypoglycemia due to an endocrine disturbance, with the exception of the pancreas. In Cushing's monograph, *The Pituitary Body*,[28] there is mentioned a case of pituitary tumor, in which the postabsorptive blood sugar was 0.0394 per cent. Wilder[29] reported a case of spontaneous pituitary hypoglycemia basing it on the small size of the sella turcica by x-ray and the physical habitus of the patient. Blumgarten[30] described three adults in each of whom he attributes the particular disturbance to be due to spon-

taneous hypoglycemia associated with an endocrinopathy. However, the evidence presented is not conclusive. The same may be said of Anderson's[31] case of tumor of the adrenal gland. The presence of a pancreatic lesion in the reported patient of Pettersson[32] and of Rabinovitch and Barden[33] unfortunately precludes their acceptance as instances where the adrenals were the causation of the hypoglycemia. Our case, furthermore, presented no symptoms indicating an endocrine disturbance, other than the pancreas.

An interesting aspect of the second patient pertains to her mental and neurologic status. At six months the child was apparently normal in physical and mental growth. Tests at nine and eighteen months indicated an apparently permanent retardation in the rate of mental growth. In addition, there was a permanent motor disturbance of an ataxic character. Also, the encephalograms at nine months (Figs. 7 and 8) are suggestive of some gross brain damage. These fixed changes can be justly assumed to indicate organic anatomic central nervous system changes.

The question as to whether the hypoglycemia is primary and the nervous system changes secondary, or whether the reverse relationship exists, or whether the two conditions are independent naturally arises. Recently, attention has been focused on metabolic disturbances in certain central nervous system lesions. With regard to heat regulation, water, fat, and carbohydrate metabolism, a fairly definite linkage has been established. On the other hand the data pertaining to the production of chronic hypoglycemia by involvement of the central nervous system is still meager and vague. Tilney[34] observed a case of chronic hypoglycemia in an adult in whom the only pathology revealed by postmortem examination was a neoplasm involving the floor of the third ventricle in the hypothalamic region. Various animal experiments[22, 23, 32] tend to show that stimulation of the vagus will increase the internal secretion from the islands of Langerhans, depressing the blood sugar. Whether organic lesion in the region of the vagal nuclei and nerves, or in the vicinity of structures closely linked up with the vagus through association fibers, can produce through stimulation persistently low postabsorptive blood sugar concentration is still problematic.

The question then arises: Can pathologic physiologic derangements manifesting themselves clinically in convulsions, tremors, twitchings, stupor, hemiplegia, and unconsciousness, if persistent and repeated as in this case, result also in progressive structural change and permanent lesions in the brain? The transient hemiplegias are suggestive of angiospastic changes, transitory ischemia, and disturbed circulation such as may lead to focal anatomic lesions in the brain. This mechanism has been discussed by Spielmeyer[40, 41] in cases of

epilepsy. Grayzel[43, 44] found that hyperinsulinism resulting in convulsions induced artificially in rabbits may produce anatomical changes in the brain.

Graham and Womack[45] state "that repeated observations have been made of hemorrhages into the central nervous system in severe induced hypoglycemia." Furthermore, in one of their cases, they report definite and permanent symptoms of central nervous change, which they attribute to the severe hypoglycemia which was allowed to continue for too long a time (Case 3). Changes in the Nissl granules of the ganglion cells in the white matter in the brain have been found in fatal cases of insulin shock.

From available evidence it is impossible to determine whether we are dealing here with a case of pancreatic hyperinsulinism resulting in secondary changes in the central nervous system or a primary neurological condition causing hyperinsulinism through vagal stimulation or with two entirely independent pathologic states. We believe that the weight of the evidence favors the first possibility. The negative operative finding does not invalidate this assumption since a minute nodule about 1 cm. in diameter (which has been found in other cases)[16, 1-12, 45, 46] or the existence of hypertrophy and hyperplasia of the islands of Langerhans can hardly be determined by mere inspection and palpation during an exploratory laparotomy.

SUMMARY

Two cases of persistent chronic postabsorptive hypoglycemia in children are described. The first child, I. S., presented a condition which is probably familial. The enlarged liver showed no glycogen but extensive fatty infiltration of the liver. There was sufficient hepatic tissue to perform its metabolic functions except that of glycogenesis. This primary failure to form glycogen from glucose, and the consequent absence of deposits of glycogen in the liver resulted in its secondary inability to mobilize the glucose and maintain a normal blood sugar level. A hypothesis is advanced for the presence of the fatty infiltration, e.g., the conversion of the glucose into fat since the dextrose could not be transformed into glycogen.

The nature of the hypoglycemia of the second child is still not definitely known. The associated organic central nervous system condition has raised the question as to whether this lesion is not responsible for the hyperinsulinism rather than that we are dealing with a purely pancreatic hyperinsulinism due to neoplasm or hypertrophy and hyperplasia of the islands of Langerhans. It is felt that, since to date there has been described no definite case of hypoglycemia due to a central nervous system lesion and since, on the other hand, there are a sufficient number of unquestionable cases of hyperinsulin-

ism due to a pancreatic lesion, we are probably dealing with pancreatic hyperinsulinism and that the central nervous system changes are either secondary or independent of the primary condition.

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A STATISTICAL ANALYSIS OF WHOOPING COUGH CASES

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THE following data were obtained while caring for 1,112 cases of whooping cough in the Contagious Department of Cleveland City Hospital from 1921 to 1932, inclusive.

Nine hundred and seventy-nine of the 1,112 patients, or 88 per cent, were under six years of age. One hundred and sixty-six patients died, a mortality rate of 14.9 per cent. Of the latter, 144, or 86.7 per cent, were under three years of age. There were a few more white females than males. The pertussis death rate was highest for the month of July when it was 30.1 per cent. Seventy-nine deaths occurred in infants under one year of age, 56 of which were due to bronchopneumonia. As shown in Chart 1, bronchopneumonia is the principal cause of death in whooping cough. The danger of this disease when it occurs during the first few years of life is clearly shown.

The appalling mortality rate of 30.1 per cent in the month of July is more than averaged downward by the lower rates of other months; the average death rate (14.9 per cent) was less than the 18.3 per cent mortality rate quoted for Glasgow Hospital for the twenty-two years ending with 1899 and less than the 18.1 per cent mortality rate of Edinburgh City Hospital for the eight years ending in 1911; it was 1.9 per cent more than the rate reported by Ker,[1] who up to 1914 had 1,841 cases with a 13 per cent mortality. Rates reported at times were 11.1 per cent for Geneva, 20.7 per cent for Lausanne, 18.1 per cent for Paris, and 23.6 per cent and 27.9 per cent for hospitals in Berlin.[1]

The mortality rate for whooping cough in our hospital series is high and quite in contrast to the more even death rate in Cleveland for the years 1922 to 1931, inclusive, althought the rate for the city cases includes hospital cases as well.

When total deaths and total cases of the city are plotted, the obvious increase in cases from the third to the eighth month of the year is notable (Chart 2). The total number of deaths by months in the entire city does not completely coincide with the total death rate of the hospital (Chart 2). The even keel of total mortality for the district, when plotted, is in decided contrast to the spiky curve of the hospital's mortality rate (Chart 3).

From the Department of Pediatrics, Western Reserve University, and the Division of Contagious Diseases, City Hospital.

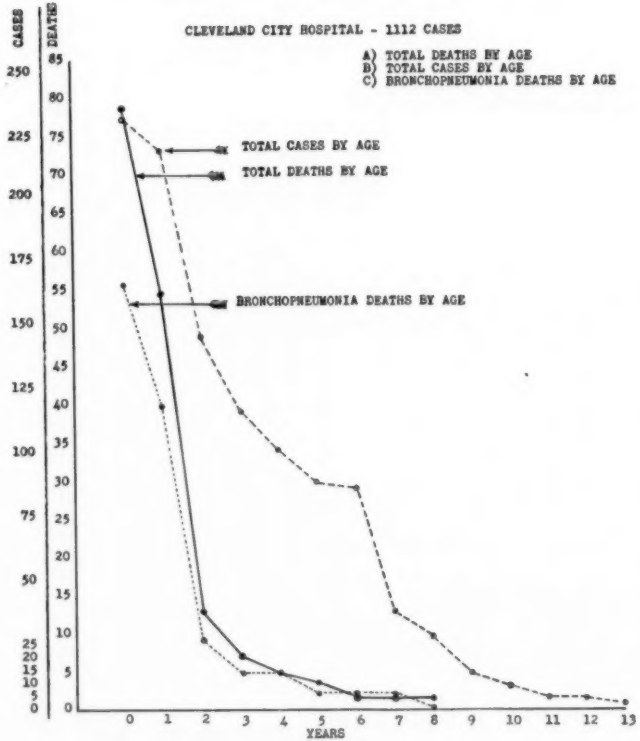

Chart 1.

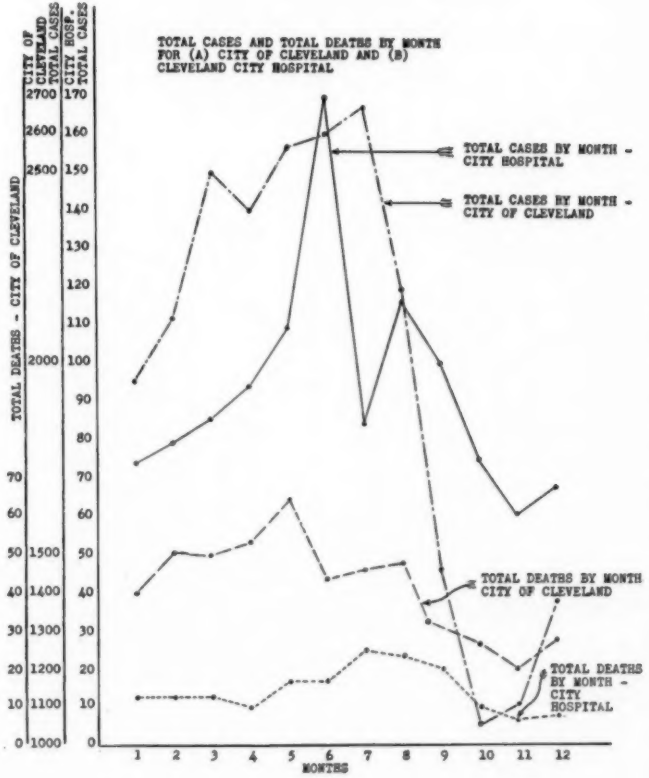
TOTAL CASES AND TOTAL DEATHS BY MONTH
FOR (A) CITY OF CLEVELAND AND (B)
CLEVELAND CITY HOSPITAL
TOTAL CASES BY MONTH - CITY HOSPITAL
TOTAL CASES BY MONTH - CITY OF CLEVELAND
TOTAL DEATHS BY MONTH CITY OF CLEVELAND
TOTAL DEATHS BY MONTH - CITY HOSPITAL
TOTAL DEATHS - CITY OF CLEVELAND
CITY OF CLEVELAND TOTAL CASES
CITY HOSP. TOTAL CASES
MONTHS

Chart 2.

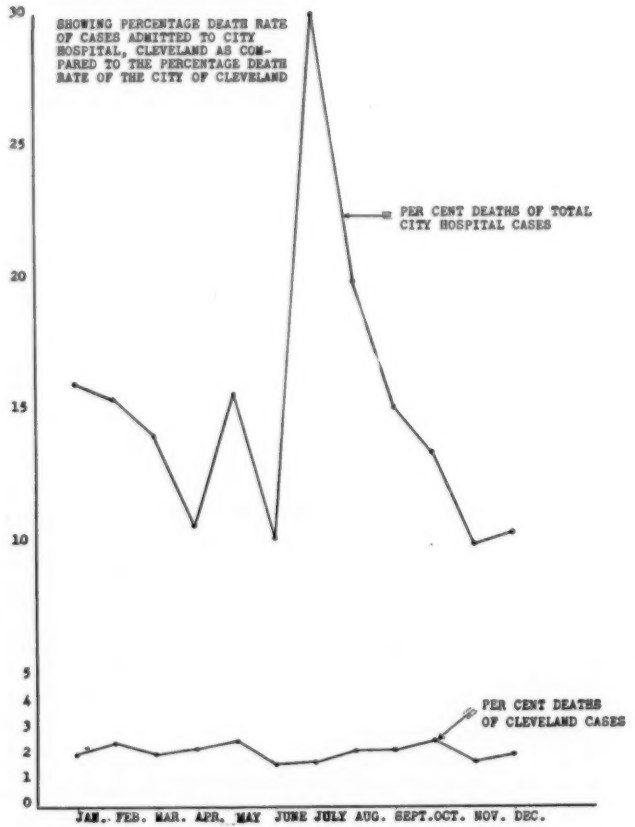
SHOWING PERCENTAGE DEATH RATE OF CASES ADMITTED TO CITY HOSPITAL, CLEVELAND AS COMPARED TO THE PERCENTAGE DEATH RATE OF THE CITY OF CLEVELAND
PER CENT DEATHS OF TOTAL CITY HOSPITAL CASES
PER CENT DEATHS OF CLEVELAND CASES
30
25
20
15
10
5
4
3
2
1
0
JAN. FEB. MAR. APR. MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC.

Chart 3.

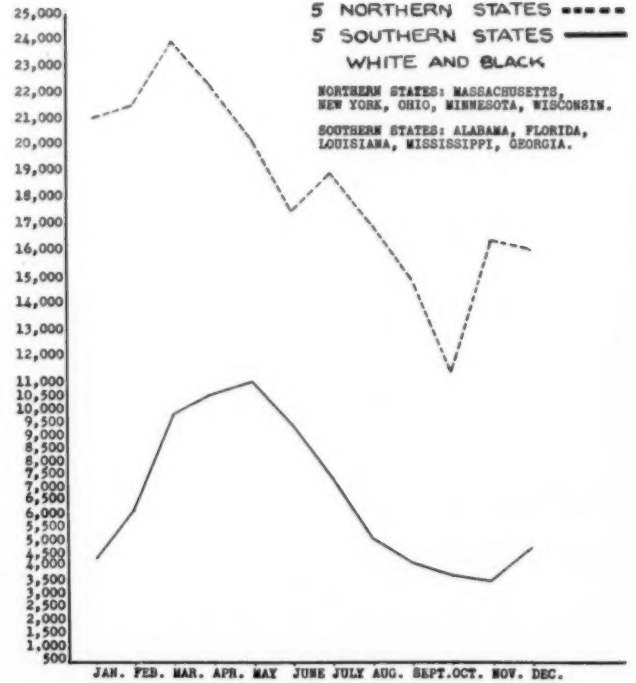

Chart 4.—Case incidence, 1925-1929.

This curve peak for Cleveland is similar in a general way to one plotted for the years 1924 to 1929 for five northern states; namely, Massachusetts, New York, Ohio, Minnesota, and Wisconsin. The same general tendency with a more even rise and fall in the number of cases is noted when the lines are drawn for five southern states, Alabama, Florida, Louisiana, Mississippi, and Georgia, for the same years (Chart 4). The deaths in the five northern and five southern states were plotted (Chart 5), and it can be seen that the greatest mortality in the five northern states is in February, March, April, and May with a rebound in August, while in the South it rises slowly in March and reaches a peak in July. There seems to be a tendency toward a southern and northern mortality seasonal incidence. Perhaps this difference is better demonstrated if the totals of both deaths and cases in the North and South are plotted, as in Chart 6.

In Ker's series, 35 per cent of the deaths occurred during the first two years of life, 22 per cent during the third year, 12 per cent during the fourth, and 8 per cent during the fifth year. Luttinger[2] reported a death rate of 50.8 per cent for the first year, 27.3 per cent for the second, 18.8 per cent for the period from the third to the fifth year, 2.7 for the period from the sixth to the fifteenth year, and 0.3 for the period from the sixteenth to the sixty-fifth year of life. In our series, 87.3 per cent of the deaths occurred during the first two years, 4.2 per cent during the third, 3 per cent during the fourth, and 2.4 per cent during the fifth year of life, our death toll being comparatively higher the first year of life.

Even though there is a high mortality rate in infancy, it has been my clinical experience as well as that of others that well-fed, healthy, sturdy infants in good surroundings actually may have few or no symptoms. Social conditions, such as poverty and inanition, create predisposing factors whose effect on the patient's general physical well-being may militate against his recovery. This is well illustrated by the fact that 35 of 92 rachitic children and 10 of 14 spasmophilic children died, accounting for 45 of the 166 deaths in our series of whooping cough cases.

The predisposing factors, together with complications of the disease, cross infections that occurred during the hospital stay, and the number of deaths accompanying each one are grouped in Table I. The severity of pulmonary complications is apparent since 122 of the 250 patients with bronchopneumonia died. Other complications seemed to have been borne well. Although practically no sequelae followed recovery in our cases, two patients died of pulmonary tuberculosis six months after an attack of whooping cough. I feel that asthma as an aftermath occurs more commonly than this hospital series would seem to indicate.

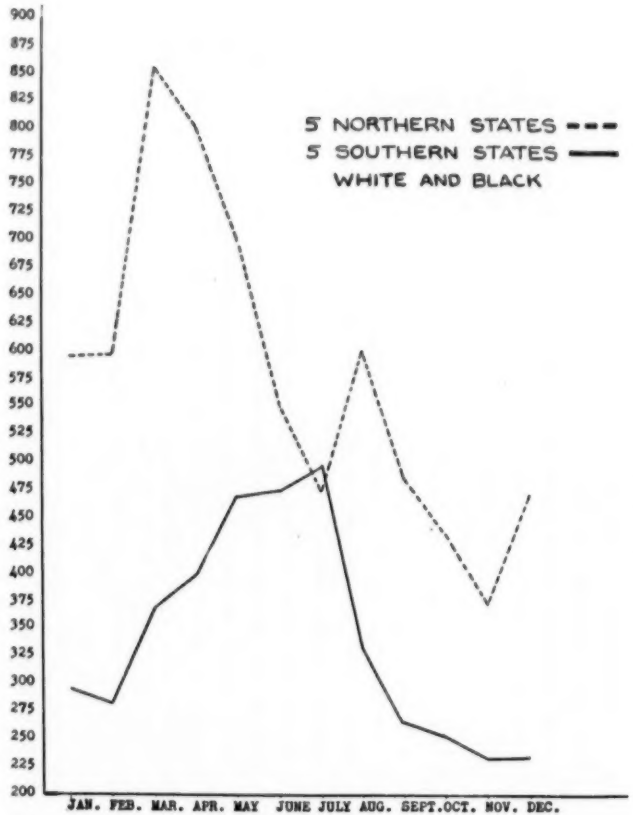

Chart 5.—Deaths, 1925-1929.

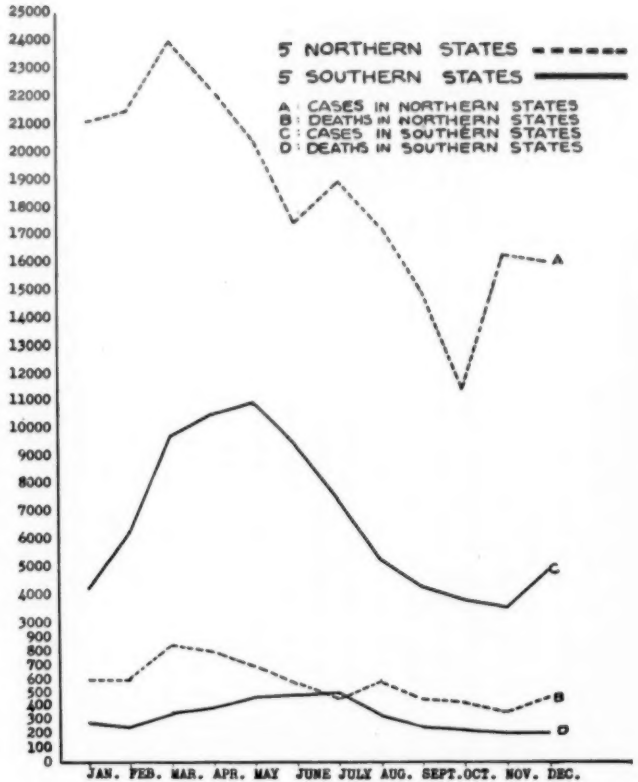

Chart 6.—Cases and deaths, 1925-1929.

Chart 7.

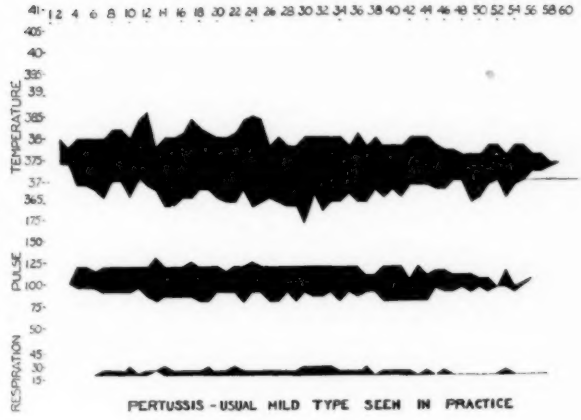

Chart 8.

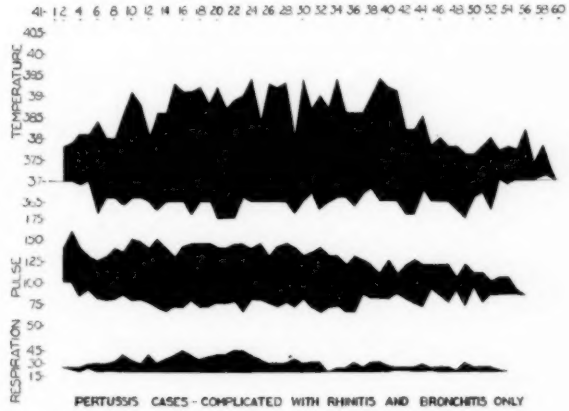

Chart 9.

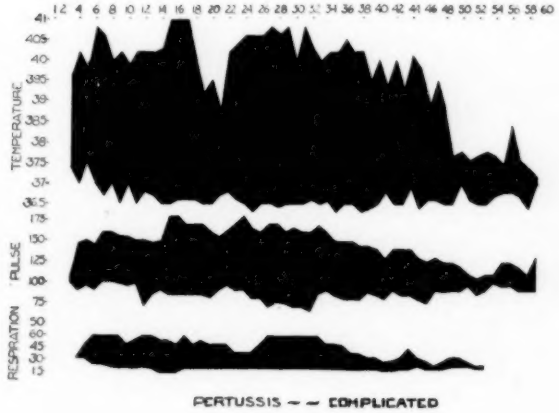

TABLE I

DISEASES ASSOCIATED WITH OR COMPLICATING 1,112 CASES OF PERTUSSIS, CLEVELAND CITY HOSPITAL, 1921 TO 1932, INCLUSIVE

CLINICAL CONDITION	PREDISPOSING	COMPLICATING	CROSS INFECTIONS	DEATHS*
1. Abscesses		7		
2. Alkalosis		3		2
3. Anemia	2			
4. Anterior poliomyelitis	4			1
5. Appendicitis		1		1
6. Arthritis		2		
7. Ascaris Lumbricoides	1			
8. Asthma		2		
9. Birth paralysis	3			0
10. Bronchiectasis		2		
11. Bronchitis	1	37		4
12. Bronchopneumonia		250		122
13. Burns	4			1
14. Cardiac dilatation		3		2
15. Cataract	1			
16. Cellulitis		1		
17. Cerebral hemorrhage		4		3
18. Cervical adenitis		7		
19. Chorea	1			
20. Colitis		1		1
21. Conjested eye vessels		1		
22. Conjunctivitis		5		
23. Corneal ulcers	1			
24. Cystitis		2		
25. Decomposition (Finklestein)		5		3
26. (Dermatitis (unknown)	2			
27. Diabetes mellitus	1			
28. Diphtheria		20		3
29. Diphtheria bacteriologically positive		7		
30. Dislocated hip	1			
31. Emphysema	1			
32. Endocarditis		(?)1		
33. Enteritis and G. I. disturbances		32		8
34. Erysipelas		1		1
35. Exudative diathesis	2			
36. Fractures—accidents in hospital		2		
37. Furunculosis	1			
38. Gonococcus infection	3			
39. Hemorrhage—conjunctiva		2		
40. Hydrocele	1			
41. Hydronephrosis	1			
42. Impetigo		10		
43. Influenza	2			
44. Intoxication (alimentary Finklestein)		4		1
45. Keratitis	2			
46. Malnutrition	13			
47. Mastoiditis	1	4		1
48. Measles	33		21	4
49. Meningitis		2		2
50. Mongolian idiocy	1			
51. Nasopharyngitis		50		5
52. Nephritis		2		1
53. Osteomyelitis	3			1
54. Otitis media		114		19
55. Peritonitis		(?)1		1
56. Pleurisy		3		
57. Pneumonia, lobar		16		

TABLE I—CONT'D

CLINICAL CONDITION	PREDISPOSING	COMPLICATING	CROSS INFECTIONS	DEATHS*
58. Pneumonia, resolving		2		
59. Prematurity	5			3
60. Pyelitis		11		
61. Pyodermia	1			
62. Prolapsed rectum		2		
63. Rat bite fever	1			
64. Rhinitis, severe		4		
65. Rickets	92			35
66. Scarlet fever			14	1
67. Scrofula	2			
68. Scurvy	2			1
69. Septicemia		2		2
70. Sinusitis		2		
71. Spasmophilia	14			10
72. Stomatitis		1		
73. Streptococcus sore throat		1		1
74. Syphilis	10			4
75. Thrush	2			1
76. Tonsillitis		5		
77. Tuberculosis. (a) Bone	2			
78. (b) Miliary	4			4
79. (c) Pulmonary	15			2
80. Umbilical hernia		12		
81. Vaccinia	1			
82. Vaginitis, nonspecific	9			
83. Varicella	1		51	

*Some of the patients who died had more than one complication.

Three charts have been prepared to show the temperature, pulse and respiration rates in each of three clinical types seen in practice. The highest and lowest temperatures, the pulse rates, and respiration are recorded daily; the shaded portions show the swings of these factors for that particular day. The first, Chart 7, illustrates the usual types of clinical reaction in the average case; the second, Chart 8, the patient who has no marked symptoms, but who has slight fever with rhinitis and bronchitis; the third, Chart 9, the stormy course of whooping cough in those cases that have complications (including data on patients that died).

NOTE.—The information for Charts 4, 5, and 6 was taken from the monthly public health reports of the United States Treasury Department. No corrections were made for errors in reporting. New York City was not included in the state of New York.

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THE OCCURRENCE OF CATALEPTIC PHENOMENA IN CHILDREN

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CATALEPSY, or waxy flexibility (flexibilitas cerea), is an abnormal condition characterized by certain peculiarities of muscular performance. The head or the limbs of a cataleptic patient remain rigidly fixed in any position in which they have been placed, however unnatural and uncomfortable. If, for instance, the arm is raised above the shoulder, it may stay there for ten or fifteen minutes or longer, sometimes even for hours, and then drop slowly, by degrees, until it resumes its original position. On passive motion, the arm usually offers a mild resistance, similar to that of a piece of wax when it is bent. If the postures of the cataleptic were assumed voluntarily by a normal individual, he would soon have a feeling of heaviness, discomfort, and fatigue and drop them after a much shorter time than the cataleptic, who maintains them without any outward signs of effort, exertion, or uneasiness.

True or genuine catalepsy, in which the patient remains entirely passive throughout, has been distinguished from pseudocatalepsy, in which the patient helps the examiner actively in placing the limb in the position which seems to be intended.

In adults, catalepsy has been observed in a variety of psychopathologic reaction forms. Its occurrence has been noted in cerebral diseases, especially in cases of epidemic encephalitis, general paresis, and cerebral abscess. It has been found on rare occasions to be a part of those mental changes which, in the form of delirium or stupor, sometimes accompany infectious and toxic diseases; short cataleptic episodes have been seen in persons suffering from typhoid fever, malaria, and acute rheumatic fever. True catalepsy or pseudocatalepsy is often a characteristic feature of the catatonic variety of the schizophrenic reaction. It is met with infrequently as an hysterical manifestation.

Cataleptic phenomena can be elicited through verbal suggestion in hypnotized individuals. A condition similar to human catalepsy has been produced experimentally in monkeys through the subcutaneous injection of bulbocapnine.

In children, particularly in infants, the occurrence of catalepsy has always been believed to be extraordinarily rare. The few references contained in the literature are listed:

From the Harriet Lane Home for Invalid Children and the Henry Phillips Psychiatric Clinic, the Johns Hopkins Hospital, Baltimore, Md.

Taupin, in 1839, wrote of a fourteen-year-old girl who was cataleptic for several hours before her death from typhoid fever.

Hirigoyen, in 1854, observed in a boy of eleven years a cataleptic condition of eight hours' duration. The patient, at the moment when his father made a move to beat him, lifted his arms in defense. He remained in that attitude until his arms were placed passively in other positions, which were also maintained for a long time.

Schwartz, in 1857, reported the case of a seven-year-old boy who, "in consequence of rough maltreatment," developed a choreic condition which was followed by a short period in which the child displayed cataleptic features.

Eulenburg, in 1877, in a monograph on catalepsy, made the general statement that the condition "has been noticed at five years of age."

Jacobi, in 1880, described definite cataleptic phenomena in a three-year-old girl suffering from typhoid fever. They were noticed during the third week of the illness and lasted at least fourteen days. "When the arms were lifted up in any position, they remained so till the child was directed in a loud voice to let them fall. The legs kept only partly in the position in which they had been placed, and soon fell. Considerable force was required to flex the extended arm." The child was rather listless and apathetic during that period.

Strümpell, in 1885, made this observation: "Fairly marked catalepsy may be seen occasionally in infants between one and two years of age, suffering from various affections. It is probably due largely to some degree of clouding of consciousness or sometimes to a sort of hypnotic condition produced by strange environment (i.e., hospitalization)."

Van Schoot, in 1887, was called to see a woman, aged forty-four years, in her seventh month of pregnancy. One day after the death of one of her children, she began having peculiar attacks in which her limbs were held in tonic contractions and remained for about ten minutes in any position in which they were placed. There was no reaction to pin pricks. In the attacks, clonic twitchings of the abdominal muscles occurred. The patient relaxed under chloroform. A week after her first attack, she gave birth to a healthy baby, whom she nursed for several days. Five days after his birth, the mother had another cataleptic attack, which was repeated a few days later, but did not come back after that. On the day when the baby was weaned from the breast, he had an attack, lasting one-half hour, in which he lay rigid, and the extremities maintained cataleptic postures for ten minutes.

Epstein, in 1896, published a series of seven cases of catalepsy observed in rachitic babies between ten months and three years of age,

all badly undernourished and underdeveloped. Almost all of them had just been through some acute illness, mostly bronchitis or pneumonia. He found the lower extremities involved more conspicuously than the upper. In two cases, the cataleptic positions were held for as long as from thirty-five to forty-five minutes. Sensibility to pain was markedly diminished. The patients were quiet, apathetic, and semistuporous.

Modigliani, in 1907, presented at the Pediatric Congress at Padua three rachitic children, aged two, three, and five years, who displayed cataleptic phenomena.

Berti, in 1904, saw cataleptic attitudes, maintained for from two to seven minutes, in a nine-year-old, mentally and physically underdeveloped girl, who had had typhoid fever at the age of five years. The author assumed that the typhoid infection had set up a condition of "cortical hypofunction."

Hecker, in 1907, reported the occurrence of catalepsy of four weeks' duration in a three-year-old boy who was admitted to the hospital because of chronic diarrhea. He had had measles and then pneumonia a few months before his admission. He was frail, undernourished, and anemic. During examinations he cried incessantly in a monotonous manner, but for the rest of the time during the first few days in the hospital he lay there listlessly and motionlessly. Sensibility to pin pricks was diminished. The child rolled his head a good deal both in his sleep and while awake; even though nystagmus was absent, Hecker felt that the head rolling was of a spasmus nutans type.

The most remarkable feature of this child's catalepsy was that it existed only in the presence of physicians and nurses. When he believed himself unobserved, he became alert, moved about normally, played with his toys, and talked to the other children in the ward. But as soon as he noticed that he was watched by an adult, he resumed his lethargic attitude, became rigid, and displayed the typical cataleptic phenomena, which decreased gradually as regards intensity, duration of the postures maintained, and frequency with which these postures could be elicited.

Fischer and Rogatz, in 1924, reported the case of a boy, aged twenty-two months, in whom cataleptic tendencies had been noticed by his mother "always." "The upper extremities may be placed in any position and they remain suspended without support. The child seemed very apathetic and somewhat dulled in his reaction to his environment. He cerebrated slowly. Nevertheless he seemed fully aware of all that was happening. He would toddle around the ward with his arms suspended in the most difficult positions and apparently pay no attention to the obvious inconvenience. These various positions of the arms and forearms were held for as long as seventeen minutes at

a time, after which there began a gradual relaxation, until the hands fell to the sides five minutes later. If an attractive object were offered to the child, with his hands above his head, he was able to grasp for the object. With the arms in different position there was a distinct resistance offered to change of position. The forearms seemed without sensation to pin pricks or excess of heat. It was possible to stick a pin through the skin into the muscle without reaction to the child. There was slight sensation over the arms. . . . The lower extremities showed cataleptic state in very slight degree only."

De Sanctis, in 1925, in his textbook, *Infantile Neuropsychiatry,* mentioned among the "little signs" of motor instability a group of reactions consisting of preservation of positions given to the arms, the legs, the head, and the trunk. He spoke of "cataleptoidism" as an expression of "psychomotor infantilism," analogous to Bernheim's "cataleptility" and Dupré's "psychoplasticity" and "motor debility." De Sanctis described "formes frustes" or "attenuated forms" of catalepsy and interpreted cataleptic phenomena occurring in the wake of infectious diseases as "schizophrenic infanto-puerile subacute post-infectious syndromes." He reported the case of a ten-year-old epileptic boy who showed definite features of waxy flexibility.

Ziehen, in 1926, in his textbook on mental diseases in childhood, mentioned the occasional occurrence of catalepsy in the delirium of infectious diseases and as a short phase in the course of hysterical major attacks.

Marinesco, Kreindler, and Cohen, in 1930, described catalepsy in a fourteen-year-old boy, occurring in the course of Sydenham's chorea. The boy had a history of convulsions in infancy, influenza and malaria at five years, diphtheria at six, pneumonia at seven, scarlet fever at eight, acute rheumatic fever at nine, with several relapses thereafter. When he was twelve years old, he had a rheumatic attack accompanied by chorea. At fourteen, he again had rheumatism, followed by chorea which was associated with typical catalepsy.

Surányi, in 1932, mentioned the occurrence of cataleptoid motility disturbances in a developmentally retarded girl, aged three and a half years, who could neither stand nor walk. There was a slight resistance to passive movements. Catalepsy of the arms was less marked than that of the legs, which maintained postures for from fifteen to twenty minutes.

Fantini and Troili, in 1932, quoted Capuzzo as reporting in 1909 the case of a boy, three years old, who was cataleptic for five months following pertussis with pneumonia. They examined ninety-six "unstable" children between six and fourteen years of age (enuretic children, tiqueurs, sleepwalkers, etc.) and found, strangely enough, "cataleptoid postures" in not less than forty-three of the patients.

In a control series of eighty "normal children" they found no cataleptoid tendencies. We were unable to substantiate these findings in our own clinical material.

We do not, in this paper, deal with the cataleptic features found sometimes as part of the catatonic pictures associated with "dementia precoccissima" of De Sanctis and "dementia infantilis" of Heller. We do, however, wish to call attention to the statement of Weygandt that in rare instances mild cataleptic phenomena may be observed as a transient phase in the motor development of normal infants.

We have had an opportunity to observe four cases of catalepsy in children at the Harriet Lane Home within the last three years. Two further cases were seen at the Harriet Lane Home in 1914, and we were in the fortunate position to examine those two patients twenty years later.

CASE REPORTS

CASE 1.—*Catalepsy in a mentally retarded, hysterical girl, nine years old, suffering from otitis media.* Mary G. was exactly nine years old when first seen at the Harriet Lane Home on May 15, 1914. She came of poor stock. Her father was a heavy drinker; he died in a psychopathic ward. Mary, her father, and two of her siblings had the habit of gritting their teeth at night to such an extent that the upper incisors were ground down almost to the gums. One of Mary's brothers now is an inmate of a state hospital for the insane. Her mother is unable to speak English although she has been in this country at least forty years.

One night in March, 1914, Mary was suddenly taken sick with a severe headache. She had fever and running ears during the following week. A nurse advised the family to send her to a hospital. Children told her that she would be cut up in the hospital. On that day, Mary began to throw her head about from side to side; this persisted for about two weeks. Then she complained of pain and stiffness in her right knee and foot. The movements of the head and the stiffness of the knee both continued.

On admission, Mary cried constantly and would not be pacified in any way. She screamed and fought the physicians and nurses. When asked to sit up, she threw her head in all directions. She would not walk but hopped about on the left leg, holding the right from the floor.

Upon examination, she was found to be a pale, well-nourished girl who had a poor posture (lordosis). The right knee was held stiffly; the condition was essentially a quadriceps spasm which could be overcome, and then the knee could be flexed easily like a flail. During sleep, on a few occasions, the right leg was found flexed; on other occasions, rigidly straight. There was ankle clonus on the right, as long as there was resistance.

On May 25, the following observations were made: The child's mouth was held in a curious position, the angles drawn outward. If the upper lip was elevated passively, there was a tendency to maintain that position. Similarly, when the jaw was opened, it remained so for some time; it was even difficult to close it. The left leg kept any position in which it was put passively, unless maintenance caused too much effort (for instance, when the hip and the knee were each flexed at a right angle). There was also catalepsy of both arms.

The temperature was slightly elevated throughout her stay at the clinic. The number of her white blood cells was 15,600. The left ear drum was perforated and discharging pus.

On May 25, 1914, Mary left the hospital against advice.

Mary is now twenty-nine years old. She reached the sixth grade in school with considerable difficulty. Then she worked in a clothing factory and spent the summers in the country, canning tomatoes. She is now married to a World War veteran, an invalid, whom she seems to give good care.

CASE 2.—*Cataleptic episodes, following febrile convulsions (otitis media, measles, mumps), occurring in an imbecile girl between the ages of three and seven years.* Mary S. was first examined at the Harriet Lane Home on October 17, 1914, at the age of three years and three months. She was the result of the eleventh pregnancy of a feebleminded mother, who was seriously ill with typhoid fever shortly before Mary's birth. The home environment was one of extreme poverty, ignorance, and poor hygiene. Pediculosis capitis was found in practically every member of the family. There was no regularity of feeding; the children received no vegetables but much tea and coffee. Mary had diarrhea during the greater part of her first year of life.

Mary had a generalized convulsion, lasting ten minutes, in July, 1914, a few days after her third birthday. She had a second convulsion on October 17, the date of her admission to the clinic. On the following day, she showed a mild degree of catalepsy which increased in intensity during the next days. On October 21, Dr. Blackfan made the following entry in the case record: "Since the first period of excitability following the convulsion, the child has been the reverse, lying in a state of apathy, paying no attention to her surroundings. She seldom speaks. At the visit of her mother she spoke fluently. Facial expression was dull, masklike. She shows a definite element of catalepsy, stands in bed for indefinite periods with arms and head in fixed positions, glancing about occasionally with head and eyes. She will hold her arm and leg in any position where placed, though sensi-

tive to pain. This stage varies, being more marked when fever is present." The child had acute otitis media of the right ear; myringotomy was performed.

On January 24, 1915, again in connection with acute suppurative otitis media, she had a severe convulsion, lasting about twenty minutes. She was cataleptic for the following five days; the catalepsy was more marked in the legs than in the arms. Both ear drums were incised, and the tonsils and adenoids were removed.

On January 17, 1916, coincident with the onset of measles, Mary again had a convulsion. It was followed by catalepsy, which was present for at least four weeks.

On June 24, 1918, coincident with the beginning of mumps, she had a severe convulsion; she was unconscious for more than an hour. Marked catalepsy was observed when she was examined in the dispensary.

Mary is now twenty-three years old. We learn that she had convulsions with every elevation of temperature until the age of thirteen years. She is a low grade imbecile, having a mental age of five years. She is totally illiterate; she did not go beyond the first grade in school. Three years ago, she gave birth to an illegitimate child, who has been treated for scurvy at the Harriet Lane Home.

CASE 3.—*Catalepsy in a normally intelligent boy, almost five years old, at the end of the third week of typhoid fever.* William M. was admitted to the Harriet Lane Home on February 6, 1932, suffering from typhoid fever. He was four years and eleven months old. He came of a healthy and stable family. His physical and mental development were normal. His illness began on January 20, 1932. He ran a daily fever, lost his appetite, became apathetic, and was restless at night after one o'clock. On admission, he was listless and walked with a wobbly, unsteady gait. His consciousness seemed clear though he replied to questions only after an answer had been repeatedly demanded of him.

On February 7, the eighteenth day of the disease, he was unusually quiet and lay in bed in a semistuporous condition. He showed an increasing tendency to hold the limbs in whatever position they were placed. The catalepsy lasted approximately thirty hours. At the beginning, all four extremities were involved. On the morning of February 8, his sensorium was clearer. He sat up in bed, looked at the comic sheets, and talked more freely than on the preceding days. His legs no longer retained the positions in which they were placed; the catalepsy of the arms was much less pronounced and gradually disappeared during the afternoon.

The temperature became normal on February 10. He was discharged in good condition on February 18. On subsequent visits to the dispensary, he was found to be a healthy, alert, and well-behaved boy.

CASE 4.—*Cataleptic episodes, coincident with angioneurotic edema, in the course of acute lead encephalitis in a three-year-old negro boy.* James J., colored, since early infancy had the habit of gnawing the paint off his crib and toys, eating the plaster which he dug out from the wall, and putting into his mouth, paper, coal, shoe polish, and "any dirt he could get hold of." When admitted to the Harriet Lane Home on August 15, 1932, at the age of three years and nine months, he showed typical symptoms of lead intoxication (lead line on gums, stippled cells, characteristic dense lines at the growing ends of the long bones). The illness had begun about five weeks prior to his admission with increasing pallor, vomiting, constipation, unsteady gait, attacks of abdominal pain, general weakness, enuresis, and mild delirious reactions. In the hospital, he lay in bed completely apathetic until August 23, when he became wildly delirious for about an hour and a half. He was drowsy and listless again, ran a mild fever, and had marked tremors. He improved slowly, except that he kept repeating over and over certain phrases addressed to him.

On September 8, at noon, he developed an angioneurotic edema of his face. At 7 P.M., he was stuporous and showed marked catalepsy. The arms remained in fixed positions for two to three minutes at a time. The head and legs were cataleptic in a smaller degree. The limbs were mildly spastic and offered some resistance to passive movements. Knee and ankle jerks was hyperactive. Ankle clonus was present, more outspoken on the left than on the right. On the next morning, the catalepsy was still present but less marked; postures were maintained for shorter periods. He was insensitive to painful stimuli.

Both the edema and the catalepsy disappeared on September 10 and both returned on September 19, almost simultaneously. During the following days, the picture changed to one of overactivity, excitement, hilariousness, jumping around in bed, destruction of the bedclothes, and chewing on anything within reach. This condition lasted until October 13, when he became quieter and the edema, but not the catalepsy, returned. Following this, he again became wild and noisy and remained so until a month after his discharge which took place on November 23. His behavior improved since then, but he had temper tantrums, wandered away from home aimlessly, and continued the habit of picking things up from the floor and eating them. Because of inadequate community facilities, he could not be removed from his home, in which the feebleminded parents were utterly incapable of training him. He now attends kindergarten; his mental age is less than three and a half years at a chronologic age of five years and three months.

CASE 5.—*Catalepsy and pseudocatalepsy in a feebleminded negro girl, eight years old, suffering from rheumatic heart disease.* Dorothy S.,

colored, was first examined at the Harriet Lane Home on May 11, 1933, at the age of seven years and nine months and was found to suffer from rheumatic heart disease (mitral insufficiency). She is the daughter of feebleminded parents; a brother, one year her senior, is considerably retarded in intellectual development. Dorothy herself was found to be feebleminded, having a mental age of barely four and a half years. She did not sit up alone until the age of two years and did not walk or form understandable words until she was three and a half years old. She had one convulsion at three years. She always sucked her thumb, picked her nose, and bit her fingernails. She masturbated until the age of almost seven years. She was always fearful, afraid of the dark, and had night terrors. She had a foul discharge from her right ear which stopped when sixteen teeth were removed in the summer of 1933.

Ever since her first dispensary visit, Dorothy was extremely listless and apathetic. Her knee jerks were hyperactive. On November 3, 1933, it was noticed that her arms remained for several minutes at a time in any position in which they were placed. Elevated postures of the arms were maintained for 90 to 120 seconds. When the arms were placed in more comfortable positions (for instance, with the hands resting on the head), they were kept there indefinitely, until she was ordered to put them down. The remark, "All right," was sufficient to cause her to change her position. This condition is still present at the time of this writing. At times, though not always, Dorothy actively helped the examiner in his attempts to move her limbs passively (pseudocatalepsy). The legs also showed slight catalepsy, but much less than the arms. Sensibility to painful stimuli was not impaired.

Dorothy was examined at the Psychology Laboratory of the Henry Phipps Psychiatric Clinic. Richter has found that adult monkeys, made cataleptic by the injection of bulbocapnine, will grasp a horizontal bar and hang freely by one hand for varying lengths of time; normally, they cannot be made to hang at all. He also found that cataleptic humans will hang much longer than normal individuals. Dorothy responded to this test by hanging sixty-five seconds.

CASE 6.—*Catalepsy of nine weeks' duration in a normally developed infant, sixteen months old, convalescing from chronic dysentery.*—Claire Z., youngest of ten children, of a healthy and stable family, was admitted to the Harriet Lane Home on November 21, 1933, at the age of sixteen months, because of chronic dysentery (Flexner). While she had spoken quite a few words and played normally at home, she did not talk and appeared apathetic at the hospital. Cataleptic phenomena were first observed on December 7. In the afternoon of the following day, she was found standing, holding with both hands to the upper horizontal bar on

the side of her bed. Her face had a masklike expression, and she showed no reaction to the approach of people. If a pencil or a cup were moved before her face, she followed the object with her eyes only but did not turn her head in any direction. She looked only to the side and downward but not upward. Her hands, arms, and either leg remained for several minutes in any position in which they were placed. There was no response to pin pricks. Only after repeated pricking or if an attempt to move her head was made, did she show a faint emotional response by screwing up her face a little as if she were going to cry, but she did not cry.

On December 8, she cried vigorously when stuck with a sharp point. When her parents came to see her in the afternoon, she cried almost incessantly but remained in the same position all the time; when they held out their hands to her, she made no effort to go to them.

On December 12, she began to show some interest in her surroundings. Her intestinal condition meanwhile had improved markedly. She was put in a push cart and seemed to be contented pushing herself about investigating the entire ward and the hall.

During the following days, she gained weight, took nourishment well, and had normal bowel movements. She became more and more alert, smiled occasionally, and had a few temper tantrums. For no apparent good reason, she would scream very hard and continue to do so until attention was paid to her. Her catalepsy persisted in the same degree. When her arms were raised above her head and she was tossed from side to side, she made no effort to balance or protect herself with her hands or arms, which maintained postures for from three to four minutes.

She was discharged from the hospital on December 24, 1933, in excellent physical condition. At home, she ate and slept well, was very playful, began to talk again, having a larger vocabulary than she had had prior to her admission; she had no temper outbursts. Her catalepsy, however, continued, becoming gradually less marked. It began to disappear early in February, 1934, and could no longer be elicited on February 13. On that day, when standardized with the Gesell test, she was found to have a normal developmental level.

SUMMARY

Following a compilation from the literature of the observation of cataleptic phenomena in children, six cases seen at the Harriet Lane Home are reported. In all patients, ranging in age from sixteen months to nine years, the catalepsy was closely associated with some infectious or toxic disease (otitis media, measles, mumps, typhoid fever, lead encephalitis, rheumatic heart disease, and chronic dysentery). In one instance, the catalepsy followed febrile convulsions; in another it was coincidental with angioneurotic edema; and in a third

definite hysterical features were present. Four of the patients were mentally retarded. In all cases, the catalepsy was part of a dysergastic reaction, that is, of those psychopathologic changes which are apt to occur in the course of infectious and toxic diseases.

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LOW CALCIUM TETANY IN THE NEWBORN

A Review of the Literature and a Report of a Case

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CONTROVERSY exists as to whether tetany occurs within the neonatal period of life. Most authors have considered tetany as nonexistent in the newborn. In 1922, Von Reuss[24] stated, "The characteristic symptoms of typical tetany have hitherto not been observed in newborn infants—either latent tetany with the triad of symptoms of Erb, Chvostek, and Trousseau, or the manifest tetany with spasms of the hands and feet, tonic and clonic convulsive seizures, and spasm of the larynx. . . . Apparently typical cases of tetany with laryngeal spasm do not occur within the first three months." Pearce[19] in Abt's *Pediatrics,* states, "Spasmophilic diathesis if ever present during the first three months is usually latent, as the classical signs of tetany are rarely demonstrable during the newborn period . . . and the classical electrical reactions of the spasmophilia are never present (in the newborn). Neither do we find the laryngospasm so often seen at a later time. Therefore, convulsions of the newborn appear to be seldom, if ever, the result of a spasmophilic diathesis." According to Holt and Howland[9] (1925), tetany "is very rarely seen in the first three months of life." Morse[17] characterizes the "first two weeks of life" as "a time at which tetany never occurs." Grulee and Bonar[6] conclude that "whether or not such a condition (tetany) may be found in the first weeks of life is doubtful." Lucas[14] states that "the symptoms of tetany are not found before the third or fourth month." As recently as 1929, Hess[8] declared that "authentic tetany of the newborn has not been described."

On the other hand, a few newborn infants have been described in the literature with the clinical symptoms of "infantile tetany." In 1913, Kehrer[12] reported a series of six newborn infants with spastic flexor contractures of the upper and lower extremities, positive Chvostek and Trousseau phenomena, irregular clonic spasms of the facial and skeletal musculature, and, in one case, increased electrical excitability. In three of these infants, the symptoms developed on the third, fourth, and sixth days of life, respectively; in two others, on the second day of life. In all five infants, the symptoms disappeared after calcium therapy. In the sixth infant (Case 3), the symptoms were manifested on the first day of life, and death occurred on the third day. However, blood calcium determinations were not made in any of the cases

so that absolute proof is lacking. Von Reuss doubts the authenticity of these cases due to the absence of laryngeal spasm.

In 1918, Wolff[25] reviewed the literature and quoted in detail a goodly number of cases in which spasmophilic symptoms had been observed during the first two months of life. To these, she added sixteen of her own cases of infants in the first four months of life, one of these being four weeks old. However, none of these came within what should be considered the newborn period. Klose,[13] one year later, discussed the subject and analyzed the cases collected by Wolff. He concluded that none of them were beyond question spasmophilic and declared that the age of two months is the absolute lower limit for the development of the symptoms of tetany.

In 1921, Nassau[18] reported on a series of thirty-six infants with active spasmophilic symptoms, but of these only seven were less than two months of age. Although the presence of electrical hyperexcitability in these seven cases was highly suggestive of tetany, actual calcium determinations were lacking.

In 1925, Powers[20] reported a case of infantile tetany in a five-week-old male infant with repeated convulsions. The electrical reactions were characteristic, and the blood calcium was found to be 5.3 mg. The patient was cured by the administration of calcium chloride per os.

In 1926, Griffith[5] reported a similar case in a seven-week-old female infant with the onset of convulsive attacks accompanied by tonic rigidity of the extremities at the age of five weeks. The blood calcium was 5.3 mg. The infant died suddenly on the fifth day of calcium therapy, the cause of death not having been stated.

In 1931, Shannon[22] reported nine cases of newborn infants with clinical manifestations of tetany. The picture presented consisted of three major symptom-complexes—peripheral excitability, generalized edema, and cerebral compression. Peripheral excitability was present in all cases and was the most important symptom from the diagnostic point of view. Generalized edema of the subcutaneous tissues was present in all but one of the nine cases; and in that one case, the weight curve showed a rapid increase suggestive of the so-called "preedema" of Feer.[2] To quote Shannon, "The response of this symptom to therapy directed at the peripheral nervous excitability, coupled with the frequency with which the two have been associated, merits the assumption that the relationship is a causative one and not merely coincidence." In seven of the nine cases, symptoms of cerebral involvement were present. In all but one, such symptoms promptly disappeared after therapy had been instituted; in the one exception, death occurred before the therapy could have been expected to have any effect. However, in only one of the nine cases was the blood calcium content determined. In this case (Case 3 of his report), the calcium content

was found to be 9 mg. per hundred cubic centimeters of serum during the active symptoms; however, active treatment had been employed before the calcium determination so that the original concentration at the onset of symptoms may have been higher. Subsequent tests showed that it was difficult to raise this value to a normal figure. However, when the symptoms finally subsided, a value of 10.8 mg. was obtained.

In 1931, Bass and Karelitz[1] reported on three unusual cases in newborn infants with hyperpyrexia, vomiting and convulsions with laryngospasm, carpopedal spasm, and a positive Chvostek sign during the first few days of life. Two of their three infants (Cases 1 and 2) had marked dysphagia and simulated a severe pyloric stenosis or obstruction. In all three patients, the symptoms promptly yielded to calcium given either intravenously or intramuscularly. Unfortunately in only one case (Case 1 of their report) was a blood calcium determination done, and the content was found to be 8.5 mg. per hundred cubic centimeters of serum.

In 1932, McGavran[16] described a case of an infant developing convulsions thirty-six hours after birth with positive Chvostek and Trousseau phenomena, carpopedal spasm and laryngospasm. A prompt response to calcium therapy took place. In this instance as well, no blood calcium determination was done so that even though clinically one of tetany, yet actually the diagnosis remained unproved.

Thus, a number of cases with the clinical picture of tetany have been reported in the neonatal period and in infants during the second and third months of life. These have been rather loosely classified in the literature within one general group as cases of "tetany in the newborn." Even as recently as 1933, Maslow[15] reported a series of five well-studied cases with lowered calcium figures under the heading of "Tetany in the New-Born." Yet of his five cases, only one was less than three weeks of age (patient in Case 3 being eighteen days old). His remaining four cases, admittedly proved cases of tetany, were five weeks, nine weeks, eight weeks, and two months of age respectively. Furthermore, in all the reports of tetany occurring within the first two months of life save for Maslow's cases and save for one case each of Griffith, Powers, Shannon (Case 3) and Bass and Karelitz (Case 1), the calcium content of the blood was not determined. Consequently, in an attempt to establish the existence of tetany of the newborn as a syndrome, two points merit consideration. First, to avoid confusion, the age limits demarcating the "newborn" period of life must be defined. Second, the criteria necessary for the establishment of the diagnosis of tetany must be specified.

The newborn period is generally considered as beginning at birth and ending at that time when certain changes have taken place resulting in an obliteration of the residua carried over from intrauterine

life—the separation of the umbilical cord, the obliteration of the lumen of the omphalomesenteric vessels and the closure of the ductus arteriosus—all of which usually have occurred by the end of the second week of life. Finkelstein[3] opens his book with the following statement: "We designate the infant as a newborn up to the moment in which, with the separation of the infantile organism from the mother, all evidences of intrauterine existence have disappeared. This period comprises about the first 14 days of life."

Von Reuss in the preface to his book, *The Diseases of the Newborn*, discusses fully the question of "How long shall a child be regarded as 'newborn'?" Referring to the day on which the birth weight is regained, he declares, "One cannot without justification take this day as the end of the newborn period. It occurs under ideal conditions about the middle of the second week; repeatedly, however, at an earlier or a later time, so that one cannot draw a sharp line by this means. . . . On general grounds, therefore, one would lay down the first two or three weeks as the newborn period, with the reservation that many children lose early the clinical characteristics of the newborn state, while in others these peculiarities persist for a longer time."

It seems fair to consider the newborn period as the first two or three weeks of life. Certainly infants older than one month are not newborns and when tetany occurs after this time, it should not be referred to as "tetany of the newborn" even though logically it may be an earlier form of what is termed "infantile tetany." It is possible that tetany may have been present from birth in a "latent" form only to be precipitated as a "manifest tetany" with clinical symptoms in the second or third month of life by some infection such as an upper respiratory infection (e.g., the "reddened throat" described in Maslow's Cases 1, 2, 4, and 5 occurring in the second and third months of life). That "latent" tetany may exist in the newborn can be shown by the case mentioned by Stevenson, Mitchell, and Koch[23] of a normal newborn infant with a positive Chvostek and a calcium content of 7.3 mg. per hundred cubic centimeters of serum, but without any clinical manifestations of tetany. The case was one of a series of fifty-five normal newborns with positive Chvostek signs reported by these workers in an effort to emphasize the fact that the mere presence of Chvostek's phenomenon in a newborn without any other signs is not to be considered indicative of tetany. While their main contention is correct, still a calcium content of 7.3 mg. in an infant without symptoms would certainly be regarded as indicative of latent tetany were the infant six months old. Assuredly it is not unreasonable to draw the same conclusion in the case of a newborn infant, particularly since the normal blood calcium content in the newborn is between 10.0 and 11.0 mg.

It may be that the same cause is operative in the production of tetany in the newborn as in infantile tetany, such as some deficiency either in the calcium-regulating mechanism or in the calcium metabolism or such as a lowered concentration of the ionizable portion of the calcium in the blood. Disturbances caused by hemorrhage into the parathyroids during labor would be more apt to play a part in tetany occurring during the first few weeks of life than in infantile tetany, even though in the second or third month of life.

It is difficult of course to draw any sharp line between tetany in the first three weeks of life and that in the second or third month. To avoid confusion in the discussion of this syndrome, the very existence of which has been subject to so much controversy, perhaps it would be best to apply the term "tetany of the newborn" only to those cases occurring within the first month of life.

As to the criteria for the constitution of proof of authenticity of a case of tetany, the commonly accepted indices are Erb's phenomenon (electrical reactions) and a lowered concentration of calcium in the serum of the blood. The electrical reactions for determining electrical excitability although in use in older infants cannot regularly be of much help in the newborn because of the difficulty in carrying out a proper test in such young subjects. Howland and Marriott[11] found that the normal blood calcium was from 10 to 11 mg. per hundred cubic centimeters of serum, irrespective of age and regardless of whether the estimations were made on placental blood or on the infant's venous blood. They demonstrated that spasmophilia is characterized by a lowered blood calcium content and that whenever this content falls as low as from six to seven mg. per hundred cubic centimeters of serum, active symptoms are liable to occur. Therefore, our main criterion in establishing a diagnosis of tentany in a newborn similar to that of the infantile tetany of the older infant is a lowered blood calcium content.

It has also been stated that whenever the blood calcium reaches as high as within 20 per cent of the normal, active symptoms will disappear. Thus if the normal blood calcium content is assumed to be 10 mg., then a content of 8 mg. should place the infant within the limit of safety, and no active evidences of tetany would be observed. However, the calcium is now conceded not to be the only factor, for cases in infants over four months of age have been observed with clinical symptoms of tetany in the presence of a calcium of 9 mg.; these infants have responded to calcium therapy. Similarly among the newborn, Shannon's third case and Bass and Karelitz' first case had active symptoms of tetany in the presence of calcium concentrations in the serum of 9.0 and 8.5 mg., respectively. Furthermore it is well known that cases of latent tetany can occur in older infants without any

clinical manifestations of tetany in the presence of a calcium concentration lowered to between 6 and 8 mg. The similar case of the normal newborn infant of Stevenson and his coworkers, without symptoms but with a definitely lowered blood calcium content of 7.3 mg., has been cited herein. It is evident that even in the newborn infant a calcium concentration as high as 8.5 or 9.0 mg. does not preclude the presence of a manifest tetany and on the other hand clinical symptoms are not necessarily present when the calcium concentration is as low as 7.3 mg.

The best explanation so far advanced to cover these departures from the average is that offered by Hess: "At times we are surprised to find a case of latent tetany with a concentration of calcium of 6 or 7 mg. or, on the other hand, a case of manifest tetany with a concentration as high as 8 mg. This lack of complete harmony between the clinical manifestations and the calcium in the blood indicates that some factor other than calcium concentration must be at work. Probably the calcium in the serum is not a reliable index of the level of calcium in the tissues. It has been suggested frequently that the important factor is not the total calcium of the serum, but the amount ionized." Ross[21] similarly suggests that "the symptoms of tetany are the result of a diminution in the ionized calcium in the blood."

When the cases of authentic tetany of the newborn are limited to those which occur in infants within the first three weeks of life in whom a lowered blood calcium content has been found, the total number of proved cases falls. To summarize, the only cases previously reported which meet the requirements for the diagnosis of active tetany in the newborn with a lowered blood calcium content are Shannon's third case, Bass and Karelitz' first case, and Maslow's third case. The only instance recorded of what may be termed latent tetany of the newborn (without clinical symptoms but with a lowered blood calcium content) is that of Stevenson, Mitchell, and Koch.

Since this paper is solely concerned with the low calcium type of tetany as manifested in the newborn, no attempt has been made to discuss other forms of tetany, such as the tetany due to hyperventilation or to an excessive administration of alkali. As pointed out by Gunther and Greenberg,[7] such tetany due to an alkaline shift in the acid-base balance shows no decrease in the diffusible calcium and is therefore probably not associated with a lowering of the concentration of the ionized calcium. Similarly, the type of tetany with a high phosphorus and normal calcium content has not been discussed. "Gastric tetany" has also been described in cases of pyloric stenosis with alkalosis resulting from the loss of chlorides secondary to profuse projectile vomiting. In the first two cases of Bass and Karelitz, since tetany resulted after excessive vomiting, it is possible that the tetany

may have been gastric in origin as suggested by the authors, but no chemical studies were made to substantiate this hypothesis.

The treatment for tetany of the newborn differs in no way from that of the older infant. Calcium gluconate or calcium chloride can be given intravenously, intramuscularly, or by mouth. Any one or all of these methods of administration may be employed. Viosterol, cod liver oil, and ultraviolet light favor better absorption of the calcium given per os. Parathyroid extract has been used by Shannon with favorable results.

Both the obstetrician and pediatrician must realize that this symptom-complex can occur in the newborn. The diagnosis will be suggested clinically by the presence of some or all of the following signs and symptoms: vomiting, hyperpyrexia, convulsions, twitches, tremors, carpopedal spasm, laryngospasm, positive Chvostek and Trousseau phenomena, and subcutaneous edema. Before intelligent treatment can be given, the diagnosis must be proved by the presence of a lowered blood calcium content. Elimination of delay is all-important. A prolonged period of projectile vomiting (as in Bass and Karelitz' cases) or hyperpyrexia with repeatedly recurring convulsions (as in the case reported herein) cannot long continue without causing serious damage and even death. Once the diagnosis is made, the therapeutic measures are definite and easily applied. Prompt amelioration of symptoms and an eventual cure should result. It is well to continue moderate doses of calcium per os for several weeks to prevent subsequent lowering of the blood calcium content and recurrence of symptoms such as occurred in Power's case.

It is of interest to note that in a recent textbook on pediatrics, L. Emmett Holt, Jr., and McIntosh[10] state rather conservatively, "Although tetany may occur even in the newly born, it is rare during the first three months of life." It seems more likely to suppose that if blood calcium determinations were made routinely on all newborn infants with convulsions of otherwise unexplained etiology, an increasingly larger number of cases of tetany would be found. The condition in the newborn assuredly is not as rare or even as uncommon as is suggested by the various textbooks on pediatrics.

CASE REPORT

R. McG., a full-term male infant weighing 4 pounds, 4 ounces, was delivered from a preeclamptic mother by Dr. Hellman at the Sydenham Hospital. The delivery was a normal one and not instrumental. The cranial sutures were widely separated, and desquamation was present over the entire body, face, and extremities. A formula of cow's milk, water, and dextri-maltose was given. The feedings were well taken, and the stools were normal. Hyperpyrexia was present during the first two weeks of life, the temperature ranging between 100° and 102° F., rising as high as 105° and 106° F. on three different days. On repeated physical examination, no cause for the fever was found. The urine was normal, and no

edema was present. Röentgen ray examination of the chest did not reveal any evidence of pneumonia. The mother's Wassermann test was negative. The desquamation was felt to be toxic in origin secondary to some hidden infection which was thought to be causing the hyperpyrexia.

The infant gained 12 ounces over its birth weight by the end of the second week in spite of the pyrexia. The urine remained normal. On the thirteenth day, while the temperature was 100.6° F., convulsive twitches of the face and of the right upper and lower extremities were noted by the nurse. Ten minutes later, similar twitches involved the left side of the body. During the next three days, no more twitches were seen but the baby vomited three times, in a semiprojectile fashion. On the seventeenth day of life, while the temperature ranged between 99° and 101.4°, marked tremors and generalized convulsions affecting the face, body, and extremities suddenly appeared. The convulsive seizures were intermittent in character, lasting for two to three minutes each time and recurring every fifteen or twenty minutes. Some of the convulsions were preceded by a suggestive "crow" (laryngospasm). Physical examination twelve hours after the onset of these generalized convulsions revealed hyperactive reflexes, markedly positive Chvostek and Trousseau signs, carpopedal spasm, and a suggestion of Kernig's sign; at times, a suggestive "crow" was heard. No edema was present. The fontanel and areas between the still gaping sutures were not full or tense. Our impression was that we were dealing with either a tetany of the newborn or with a meningeal irritation from a possible cerebral hemorrhage. A spinal tap was made, but no fluid was obtained. On cisternal tap, a small amount of clear fluid under decreased pressure was obtained, which was normal on examination. Unfortunately, the baby was seen late at night, and since an immediate chemical examination of the blood could not be carried out conveniently, it was decided to treat the infant symptomatically for tetany of the newborn. Thus twelve hours after the onset of the repeated attacks of convulsions, 1 gm. of calcium gluconate (10 c.c. of a 10 per cent solution) was given intravenously and 0.7 gm. intramuscularly. The same doses were again given the next morning. The convulsions became less frequent and finally ceased together with the larynospasm within the next twenty-four hours, but the tremors of the extremities, the carpopedal spasm, and the positive Chvostek and Trousseau signs persisted.

The general clinical improvement following the calcium therapy seemed to favor the provisional diagnosis of tetany of the newborn. Thirty-six hours after the onset of therapy, blood was drawn for a calcium and phosphorus determination, and a third dose of the gluconate was given intravenously. Chemical analysis revealed a calcium concentration of 7.4 mg. per 100 c.c. of serum, which substantiated the diagnosis of tetany. The phosphorus was not determined because of an insufficiency of serum. Intensive calcium therapy was then carried out intravenously, intramuscularly, and per os. Viosterol was given to increase the absorption of calcium through the intestine. The twitchings gradually subsided during the next three days, and the positive Trousseau and carpopedal spasms disappeared. The "crow" had not been heard again after the second intravenous injection. Occasional tremors of the fingers and toes were seen when the baby was moderately disturbed or when the soles or hands were pricked. The Chvostek remained positive for about one week after the onset of therapy.

The infant continued to gain weight. It slept quietly and took its feedings well. A second chemical examination on the fifth day of the intensive calcium therapy revealed a rise in the concentration of the calcium to 8.2 mg. per 100 c.c. of serum. The phosphorus content was found to be 10.5 mg. per 100 c.c. of serum.

Röentgenogram examination of the long bones and skull did not reveal any abnormal findings. The cranial sutures were found to be gradually closing on physical examination from day to day.

Unfortunately, convalescence was delayed by the appearance, at the end of a week of therapy, of an induration of the right buttock and thigh at the site of the repeated daily intramuscular injections. The intramuscular injections were discontinued, and calcium gluconate and viosterol were given per os. Daily ultraviolet irradiations were likewise given to promote the absorption of calcium through the intestinal tract. The small indurated area on the buttock broke down after two days of local applications of wet dressings. The temperature rose to 102° F. and after twenty-four hours, a seemingly fluctuant area was incised and a slight serosanguineous discharge was expressed, following which the induration gradually resolved and the wound healed. A third calcium determination on the tenth day of therapy revealed a heightened calcium content of 9.5 mg. with a phosphorus content of 7.4 mg.

At the age of four weeks, the hemoglobin was found to be 65 per cent (Sahli), and a transfusion of 80 c.c. of whole blood was given. The general condition was excellent. The infant had gained almost three pounds by the time it was discharged from the hospital at the age of seven weeks. The infant was followed up to the age of ten weeks without recurrence of any of the symptoms or signs of tetany; during which time calcium gluconate had been continued orally together with viosterol in order to maintain the level of calcium in the blood.

COMMENT

The case reported may be regarded as an authentic one of tetany of the newborn. The hyperpyrexia present since birth was probably part of the tetany symptom-complex similar in character to the hyperpyrexia in Bass and Karelitz' cases. Two attacks of transient convulsions occurred on the thirteenth day of life, but the complete train of symptoms occurred on the seventeenth day with the cardinal signs and symptoms of tetany: laryngospasm, although not constant; carpopedal spasm; positive Chvóstek and Trousseau signs; convulsions and tremors. We cannot venture any explanation for the generalized desquamation noted at birth.

In spite of thirty-six hours of intravenous and intramuscular calcium therapy, the serum calcium on the nineteenth day of life was 7.4 mg. and on the fifth day of intensive therapy, the serum calcium had risen to only 8.2 mg. with a phosphorus of 10.5 mg. Conceivably, the serum calcium may actually have been even lower than 7.4 mg. when the convulsions were noted originally on the thirteenth and the seventeenth days of life. The convulsions and laryngospasm yielded promptly to intravenous and intramuscular therapy; the tremors and twitches, more gradually; the last sign to disappear was the Chvostek. The electrical reactions were not determined due to the difficulty in carrying out the test on so young an infant.

The last two blood analyses (on the fifth and tenth days of calcium therapy, respectively) were made by Dr. Alfred F. Hess, with whom the author had discussed the case after the first chemical analysis at

our hospital laboratory had revealed a lowered calcium content of 7.4 mg. Dr. Hess, declaring that he had never seen a case of tetany in a newborn infant, had expressed his doubts as to its existence. However, after the blood analyses in his own laboratory, he stated that in his opinion the case reported herein was an authentic one of low calcium tetany and that it was proof that the syndrome can exist in the newborn infant.

One further point is of interest. The infant was born of a pre-eclamptic mother. Some of the cases described in the literature with clinical symptoms of tetany have been born of eclamptic or pre-eclamptic mothers. It is possible that this may have some etiologic significance.

CONCLUSIONS

1. Tetany of the newborn is a syndrome which can and does occur although its existence in the neonatal period has been fairly universally denied by most pediatricians.

2. The newborn period may be arbitrarily designated as the first three weeks of life. Tetany may occur at any time during this period.

3. Tetany of the newborn may exist either in the manifest (active) form with clinical symptoms or in the latent form without clinical symptoms.

4. Manifest tetany of the newborn may be characterized by any or all of the following symptoms and signs: projectile vomiting due to cardiospasm, hyperpyrexia, convulsions, tremors and twitches of the extremities, laryngospasm, carpopedal spasm, and positive Chvostek and Trousseau phenomena.

5. As with tetany in older infants, the best criteria for the presence of tetany are muscular hyperexcitability, as evidenced by a change in the electrical reactions to the galvanic current (Erb's sign), and a lowered blood calcium content. Electrical reactions are too difficult to determine properly on a newborn infant to make this sign of as much diagnostic value as in older infants, so that the sole practical proof of the diagnosis of tetany in a newborn rests with the presence of a lowered blood calcium content.

6. The diagnosis of tetany in a newborn with the previously outlined symptom-complex must be made promptly and verified by calcium determinations on the blood so that immediate therapy may be instituted. The symptoms in a case of tetany with a low serum calcium respond quickly to intensive calcium therapy (intravenous, intramuscular, and oral). Para-thor-mone has been used successfully. Viosterol and ultraviolet light should be given at the same time as the oral calcium medication in order to favor the absorption of calcium from the intestinal tract.

7. Every case of otherwise unexplained convulsions in a newborn infant should be investigated chemically to rule out tetany of the newborn. If calcium determinations were taken routinely on such infants, it is probable that tetany would be found to be much more common in newborn infants than has been previously suspected.

8. The only recorded instance of latent tetany in the newborn is that of Stevenson, Mitchell, and Koch's case of a normal newborn infant without clinical symptoms but with a serum calcium content of 7.3 mg.

9. Only three previous cases have been reported with sufficiently low blood calcium content during the first three weeks of life to warrant consideration as authentic instances of active tetany of the newborn.

10. The case reported herein with a lowered blood calcium of 7.4 mg. is the fourth reported instance of active tetany of the newborn occurring within the first three weeks of life.

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MONGOLOID IMBECILITY IN THE MONGOLIAN RACES

Report of Two Cases in Chinese Children

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REPORTS of mongoloid imbecility in the oriental races have been rare indeed in the occidental literature. The first cases were described almost simultaneously in 1922 by Tumpeer[1] in America and Demuth[2] in Germany, who reported typical mongoloid imbeciles in Chinese patients. Brousseau[3] mentions only three instances of the disorder in Chinese patients and one in a Japanese child.[4] More recently Hill[5] has reported two Japanese children who were described as typical mongoloid imbeciles. In the Japanese literature, however, there are several reports. Okashima,[6] in a study of roentgen ray measurements of the skull in various conditions, included reports of four mongoloid imbeciles, and Washio[7] made a study of mongolism based on fifty cases seen in the Children's Clinic of the Kyoto Imperial University in fifteen years. Yasui[8] and S. Arai[9] also, in reporting cases, have commented on the frequency of the condition in Japan. Yasui said that there were one or two examples each year in his clinic while Arai said that he had seen five or six such children in a period of two and a half years. Other apparently typical mongoloid imbeciles have been reported by Fukamizu,[10] K. Arai,[11] Takatsu,[12] and Arima[13] while less clear-cut examples of the disorder, in each case complicated by congenital syphilis, have been reported by Hayashi,[14] Somekawa,[15] Murauchi,[16] and Tanaka.[17*] Although these authors describe their patients as typical examples of mongolism, many of the reports, being merely abstracts of papers presented before local medical societies, are so brief that an opinion as to the accuracy of the diagnosis is impossible. In Somekawa's report, the patient was said to have had extremely free joint articulations, a small, flat nose, hydrocephalus, but no epicanthus. No Wassermann reaction was taken of the patient's blood, but his mother and elder brother were syphilitic. The child probably was not a mongoloid imbecile.

In none of the Japanese reports is mention made of the race of the patient. However, as the number of foreigners living in the Empire is not large, and as the patients were all seen in Japanese hospitals by Japanese doctors, the probability is that most, if not all, of them were Japanese. This assumption is strongly affirmed by Dr. Kusama.[18]

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There are no reports of the condition in oriental patients in the Chinese literature. Moreover, in over 280,000 out-patients seen in the Peiping Union Medical College Hospital since its opening, only five instances of mongoloid imbecility have been encountered. One of these patients was the daughter of a Scotch mother and a Chinese father. The other four were pure-blooded Chinese. All are described as being typical mongoloid imbeciles or idiots. As the details of the dispensary records are not complete, only two cases that came under the direct observation of the author will be presented in detail. The infrequency of such reports and the desirability of recognizing that the condition is not rare among orientals make this paper seem justified.

Fig. 1.—Case 1. The physiognomy is that of a typical mongoloid imbecile. There is marked hypermotility of the joints.

CASE REPORT

CASE 1.—Y. H. C., a Chinese female child, two years and two months old, was brought to the hospital on October 19, 1932, because of failure to develop normally. Her father and mother, each aged thirty-five years, were well. They both were pure-blooded Chinese. The mother had had three pregnancies. The first ended with the birth of a boy who was apparently normal at the age of six years. The second was terminated by a miscarriage following exertion after three months' gestation, and the third resulted in the birth of the patient. There was no history of mental disease, syphilis, or tuberculosis in the family.

The patient was born at term by an easy, spontaneous delivery. There were no recognized abnormalities in the neonatal period. She was fed on an adequate dried milk-carbohydrate-water formula. Cereals and other solid foods were added to her diet after the seventh or eighth month of life. Cod liver oil and orange juice were given in sufficient dosage. The child's development was considerably

delayed. She was able to sit alone at the age of ten months. At the age of fourteen months she could stand alone and could say single words. Her teeth began to erupt at the age of seven months. However, when she was twenty-six months old she had erupted only fourteen teeth, she was unable to walk, and she still could say only single words. Her parents felt that she was definitely subnormal mentally.

She was fairly well developed physically and was well nourished. She was happy and contented, was easily amused, but showed no power of concentration and little interest in her surroundings. Her facial expression was rather vacant, and she appeared to be much delayed in mental development.

Fig. 2.—Case 1. The hands are broad and short with incurved little fingers.

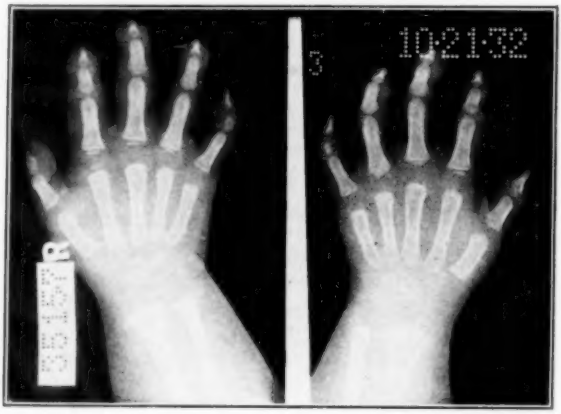

Fig. 3.—Case 1. Roentgenograms of the hands. The second phalanx of the fifth digit of each hand is short, wide, and irregular in shape, with markedly deficient calcification.

Her head was normal in configuration. The anterior fontanel was open, one centimeter in diameter. The growth and texture of her hair were normal. The patient's physiognomy was that of a typical mongoloid imbecile (Fig. 1). The eyes were slightly sloping with a heavy epicanthus. The nose was flat, saddle-shaped, with wide anterior nares. The mouth was usually open. The tongue was normal in size. The teeth, fourteen in number, were apparently normal. The heart, lungs, and abdomen were normal and showed no evidence of congenital defects. The muscles were extremely hypotonic and there was marked hypermotility

of all the joints in the extremities. The legs could easily be extended along the trunk until the feet were beside the face. The feet could be dorsiflexed until the great toe touched the anterior aspect of the tibia, and the fingers could be made to touch the dorsum of the forearm without great difficulty. The hands were broad with short fingers, the shortening being more marked with the thumbs and little fingers. The little fingers were typically incurved (Fig. 2). There was no unusual widening of the fissures between the great and second toes.

Laboratory examinations of the blood and urine gave normal results. Roentgenograms of the bones of the extremities showed moderate generalized osteoporosis. The centers of ossification were irregularly developed, those in the tarsus being normally ossified for a child of over twenty-eight months while those in the wrist indicated a bone age of under fifteen months. The second phalanx of the fifth digit of each hand was short, wide, and irregular in shape, with markedly deficient calcification (Fig. 3).

The child was under observation in the hospital for one week. Immediately after her discharge she and her parents moved from Peiping. Further observation has been impossible.

CASE 2.—L. T. H., a Chinese female infant, was brought to the hospital on September 23, 1933, at the age of two days, because she had been found to have no anal orifice. Her father and mother, each aged forty years, were well. They both were pure-blooded Chinese. The mother had had six pregnancies. The first, second, third, and fifth resulted in the birth of apparently normal children. The fourth resulted in a miscarriage after three months' gestation, and the sixth resulted in the birth of the patient. The oldest sibling was twelve years old, the youngest two years old. There was no history of mental disease, tuberculosis, or syphilis in the family.

The patient was born spontaneously at term. It was noted at the time of birth that there was no anal orifice. No other defect was noted. A roentgenogram of the abdomen taken after admission showed that there was considerable gas in the intestines. The rectum was well distended and extended to within 2 mm. of a probe in the dimple of the proctodeum. A plastic operation, by which an artificial anus was established, was performed immediately after admission. The infant passed meconium and stools normally, responded well, and gained weight. In view of the difficulty attendant upon the artificial feeding of small infants in China, and the desirability of establishing an adequate supply of breast milk in the mother, the patient was discharged four days after operation. At that time she was in good condition.

She failed to return for follow-up examination within the next month. She did well, however, until from October 17 to 20, 1933, when she failed to pass any stools. During the succeeding two or three days she passed normal stools but beginning October 23 she suffered from obstipation. Her abdomen became markedly distended three days after the onset of obstipation, and the following day, October 27, she was readmitted to the hospital. The anal orifice was entirely closed, and the abdomen was distended to an extreme degree. An enterostomy and a second plastic operation, reestablishing an anal orifice, were performed immediately. The patient responded well and, until her last visit to the out-patient clinic on November 30, 1933, had had no more difficulty from her surgical condition.

At the time of her second admission, however, careful observation revealed that the patient had all the characteristics of a typical mongoloid imbecile (Fig. 4). Her head was brachycephalic in type. She had a pronounced epicanthus, small saddle nose with wide anterior nares, and an open mouth. Her tongue was normal

in size. Her heart was enlarged both to percussion and by roentgenogram, and there was a loud, blowing systolic murmur heard with the greatest intensity just inside the left nipple. The lungs and abdomen were normal.

Fig. 4.—Case 2. The facial features and the shape of the hands are characteristic of those seen in mongoloid imbeciles.

Fig. 5.—Case 2. Roentgenograms of the hands. The second phalanx of the fifth digit of each hand is extremely short.

The muscles of her extremities were poorly developed and were hypotonic. The joints were loose and hypermotile; the feet could be dorsiflexed until the great toe touched the anterior aspect of the tibia, and it was quite easy to obtain an impression of the center of her palm. The hands were broad with short fingers, the shortening being most marked in the thumbs and in the little fingers. The

latter were incurved, and were so short that they did not reach to the second interphalangeal joints of the ring fingers. There were wide fissures between the great and second toes, and the skin of both the palms and soles was deeply fissured.

Laboratory examinations of the patient's blood and urine were normal. A Mantoux test was negative, as were the Wassermann and Kahn tests on the blood serum. Roentgenograms of the extremities showed shortening of the second phalanx of the fifth digit of each hand (Fig. 5). The other bones appeared to be normal.

The patient was discharged from the hospital on November 10, 1933. She was followed for one month during which time there was no change in her condition.

COMMENT

The diagnosis of mongoloid imbecility in these patients seemed quite certain. It is true that the second patient lacked the final confirmation of the diagnosis—obvious idiocy with advancing age—that time alone can give. But both patients exhibited the typical features of the condition to such an extent that, while they were strikingly different from normal Chinese children, it might have been difficult to make a racial differentiation if they had been placed in a group of mongoloid imbeciles of Caucasian parentage. The child in Case 2 also had two other congenital anomalies which are frequently associated with this condition, and in each case there were roentgenologic changes in the bones similar to those first described by Smith[19] and now accepted as offering confirmatory evidence of the diagnosis of mongoloid imbecility.[3, 20, 21]

In less striking examples, however, the diagnosis might be more difficult. We have seen other imbecilic patients in whom the physiognomy, the shape of the hands, the roentgenologic changes in the bones, or other single characteristics were quite typical. In Caucasian patients these, in association with other perhaps less marked features, might have been considered diagnostic. But, as West[22] showed with regard to the shape of the hand, there is no single feature that gives pathognomonic evidence of mongolism. Consequently, it is safe to make such a diagnosis, especially in oriental races, only when a clear-cut picture, such as those described above, is presented.

The rarity of reports of the disorder in Chinese patients can be in part accounted for by this fact. But of perhaps equal or greater importance is the reticence of the poorer Chinese in consulting "western" or modern physicians. These patients, being quiet and not acutely ill, may be kept at home without medical attention throughout their lives. Only by the well-to-do or more highly educated families will a physician be consulted about the children's mental status. If a complete survey were possible, perhaps mongoloid imbeciles would be found to be much less uncommon in China than is thought to be the case at present.

SUMMARY

The case histories of two Chinese children with mongoloid imbecility are presented in detail. Three similar children, one a Eurasian, are mentioned. A brief résumé of the literature of this condition in mongolian

races is made. With the publication of this report there are six definite instances of mongolism in Chinese and sixty or more in Japanese patients recorded in the literature.

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PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

Further Observations of the Therapeutic Effects of Glycine and Other Substances Used in the Treatment of Fourteen Cases of Muscular Dystrophy

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BRAND, Harris, Sandberg, and Ringer[1] in 1929 reported the effects of various amino acids on the rise of creatinine excretion. These metabolic studies were confirmed by Thomas, Milhorat, and Technor[2] in 1933. In addition, these latter writers reported the beneficial therapeutic effects of the administration of amino acetic acid, or glycine,[3] in a few cases of pseudohypertrophic muscular dystrophy. This was followed by a widespread trial of this substance in all diseases primarily involving the muscles.

The most beneficial results have been reported in cases of pseudohypertrophic muscular dystrophy by Thomas, Milhorat, and Technor,[2] Kostakow and Slauck,[4] in the German literature, and by Beard and Tripoli[5]; Chanutin, Butt and Royster[6] in this country. Less favorable results with the glycine treatment in muscular dystrophy have been reported by Brand and Harris,[7] Boothby,[8, 8a] and by our own clinic.[9] Other workers[1, 7, 8, 10] have observed the metabolic effects of glycine in other muscular diseases without reporting any beneficial results except in the cases of myasthenia gravis, reported by Boothby[8] and Remen.[11]

Most reports have based their conclusions largely upon the clinical observations of the physical functions of the muscle, the subjective symptoms, and the metabolic changes found in the urine. Recently Reinhold, Clark, Kingsley and Custer[12] have given a report on the chemical and microscopic changes in the muscles of eight cases of pseudohypertrophic muscular dystrophy treated with glycine. They noticed little clinical improvement but reported a few cases where microscopic examination showed some slight regeneration of the muscle sections, and the chemical studies pointed to a moderate degree of recovery. Objective animal experiments were reported by Lillie.[13]

In November, 1932, our clinic took up the work as reported by Thomas, Milhorat, and Technor,[2] and our preliminary report[9] was submitted in February, 1933. Since that time we have been able to follow the glycine treatment and the metabolic studies of fourteen cases with the

From the Department of Pediatrics, Indiana University Medical School.
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Animal experiments and observation with theelin were performed by Maurice V. Kahler, M. D.

following observations and results. Since our first report a large number of cases were followed, but only those who have been studied more intensely from both the metabolic and the therapeutic standpoint are included in this report.

I. METHOD OF ADMINISTRATION

The product used was chemical glycine,[3] or amino acetic acid (NH_2CH_2COOH), which was given in a dosage of 7½ gm. dissolved in two ounces of water twice a day. When we gave it orally, we noticed no toxic effect from the administration of this drug over long periods of time. In a few cases we administered the drug intravenously with no therapeutic or toxic effect. Since we found no particular advantage of the intravenous method over the oral method, the former was soon abandoned. The dosage of glycine is by no means settled and will require further study over long periods of time to determine whether or not this dosage is adequate.

II. DIET AND LABORATORY

These patients were all admitted to the hospital for metabolic study, placed on a diet containing from 75 to 100 gm. protein, and observed for a period of ten days. They were then discharged with definite instructions as to diet and medication. Once a month they returned for clinical observation and twenty-four-hour urine studies. Urine samples were analyzed for creatine and creatinine by the Folin method.[14]

III. CRITERIA NOTED FOR IMPROVEMENT

1. *Local Motion.*—Any improvement noticed in performing certain outlined movements was observed and recorded. Nine cases were ambulatory before treatment, and five were wheel chair cases. These cases were also followed by motion pictures taken at monthly intervals. In no case did we notice striking improvements in motion although the parents and teachers of patients in Cases 9, 10, 12, and 13 reported that these children were much more active in play and in handling themselves. One patient (Case 13), who was totally helpless before treatment, was able to hold a book and propel himself in a wheel chair after one month of treatment.

2. *Sensations.*—In none of the cases observed were we able to get a history of subjective symptoms, such as the crawling sensation in the muscles as reported by Milhorat and Technor.[2]

3. *Ergographic Tracings.*—Any slight improvement in the pull of the arm or leg muscles was charted by the method shown in the chart in the preliminary report (J. PEDIAT. **3**: 355, 1933).

4. *Summary of the Above Observations.*—This is shown in Table I.

TABLE I

TOTAL NUMBER OF CASES OBSERVED FOR A PERIOD OF ONE YEAR—14

NUMBER AND TYPE	IMPROVED	STATIONARY	PROGRESSIVE
Early cases—1	1	—	—
Moderately advanced cases—8	1	6	1
Advanced or wheel chair cases—5	1	1	3
Total	3	7	4
Percentage	21.4%	50%	28.6%

IV. METABOLIC OBSERVATIONS (CHART I)

1. *Creatinine Excretion.*—In all cases studied it was found that creatinine excreted daily was low for age and weight. In no case did

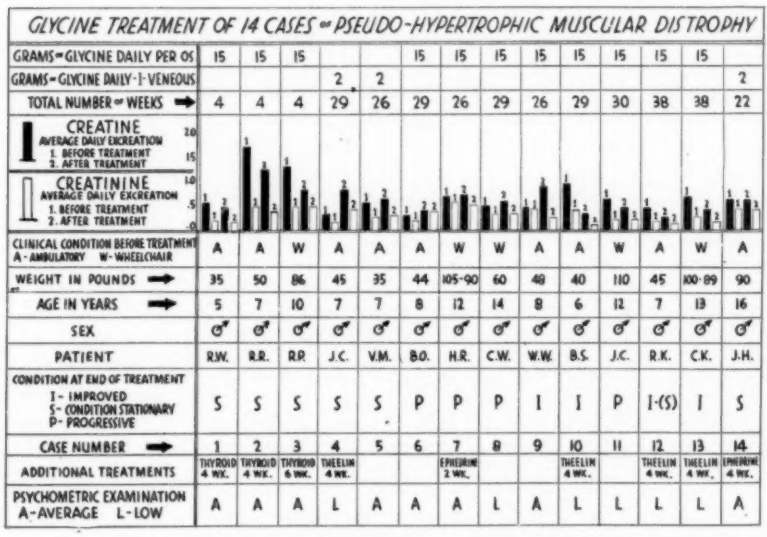
GLYCINE TREATMENT OF 14 CASES OF PSEUDO-HYPERTROPHIC MUSCULAR DISTROPHY
GRAMS OF GLYCINE DAILY PER OS
GRAMS OF GLYCINE DAILY I. V. ENEOUS
TOTAL NUMBER OF WEEKS
CREATINE AVERAGE DAILY EXCREATION 1. BEFORE TREATMENT 2. AFTER TREATMENT
CREATININE AVERAGE DAILY EXCREATION 1. BEFORE TREATMENT 2. AFTER TREATMENT
CLINICAL CONDITION BEFORE TREATMENT A - AMBULATORY W - WHEELCHAIR
WEIGHT IN POUNDS
AGE IN YEARS
SEX
PATIENT
CONDITION AT END OF TREATMENT I - IMPROVED S - CONDITION STATIONARY P - PROGRESSIVE
CASE NUMBER
ADDITIONAL TREATMENTS
PSYCHOMETRIC EXAMINATION A - AVERAGE L - LOW
R.W. R.R. R.R. J.C. V.M. B.O. H.R. C.W. W.W. B.S. J.C. R.K. C.K. J.H.
THYROID 4 WK. THYROID 4 WK. THYROID 6 WK. THEELIN 4 WK. EPHEDRINE 2 WK. THEELIN 4 WK. THEELIN 4 WK. THEELIN 4 WK. EPHEDRINE 4 WK.

Chart 1.—Glycine treatment of fourteen cases of pseudohypertrophic muscular dystrophy.

we note any appreciable rise in creatinine excretion during the long period of glycine administration. In a few cases there was a slight lowering of the creatinine excretion under treatment.

2. *Creatine Excretion.*—The relative amount of creatine excreted was increased in all cases. A study of the black No. 2 columns in Chart 1 shows some decrease in the creatine excretion after prolonged treatment with glycine, but in no case was the drop a marked one. We have been unable to observe any marked drop of creatine excretion associated with the rise of creatinine and an associate clinical improvement, as reported by Milhorat and Teehnor[2] following glycine therapy.

V. OTHER OBSERVATIONS

1. *Psychometric Examination.*—It is to be noted that six of the fourteen patients (42.8 per cent) studied were below normal, according to our psychometric standards. In our previous report[9] we noted 33 per cent of the case histories studied showed the patients to be below normal mentality. A separate study of the creatine and creatinine metabolism in a large group of normal children and of low normals is in progress at this time in our clinic. This will be reported later.

2. *Weight.*—In all of our cases there was a tendency to lose weight. In two wheel chair cases (Cases 7 and 13) the weight loss was 15 and 10 pounds, respectively. This may have been due to a calculated diet or to increased activity on the part of the patient.

3. *Sex.*—In all cases studied and in all histories studied, it was noted that the patients were all males. In studying the literature, most reported cases were of the masculine sex. Wherever a case in the female was reported, there was a doubt as to the true diagnosis. Because of the predominance of muscular dystrophy in males, we have attempted to study four cases who have received theelin in addition to glycine. (See below.)

VI. ADDITIONAL TREATMENTS

1. *Drugs.*—The effects of such drugs as pilocarpine,[15] phosphorus and ephedrine have been tried, with negative results.

2. *Glandular Products.*—The rôle of the endocrine glands in muscular dystrophy has been suggested by Janney, Goodhardt and Isaacson[16] and by the predominance of the male sex, as noted in the above paragraph.

A. Theelin: Five male patients in our series have been treated with the ovarian hormone, theelin. Each child was given fifty rat units a day of the watery preparation. Theelin was extracted from the urine of these patients and injected into experimental animals. Of this group, only one of the animals showed estrus. Cases 4, 10, 12, and 13 have shown some clinical improvement on the combined treatment.

According to Dodds,[17] the potency of the watery preparation of theelin is doubtful. We were, therefore, unable to draw any conclusions from these five cases. We have prepared a preparation of theelin in oil (50 rat units per cubic centimeter) which we are now using in our experimental observations. The results of this work are to be published later.

B. Insulin: Because of the observations of Janney, Goodhardt and Isaacson[16] of delayed glucose utilization in muscular dystrophy and the chemical changes in the blood and urine as noted by McCrudden and Sargent,[18] two of our workers[19] tried the effects of high carbohydrate diet plus large doses of insulin, with negative results in a series of six cases.

C. Thyroid: The relation of thyroid and creatine metabolism has been mentioned by Janney, Goodhardt and Isaacson.[16] Poncher[20] also has noticed the beneficial effect of thyroid therapy on the creatine metabolism of a case of myatonia congenita (Thomsen's disease). Thyroid therapy in four of our cases showed no therapeutic effect or metabolic change in the urine to any appreciable effect. Cases 2 and 3 did show some decrease in creatine output, but little clinical improvement.

SUMMARY

1. The metabolic and therapeutic effect of glycine and other substances has been reported in fourteen cases of pseudohypertrophic muscular dystrophy, with comments on our early observations of a few cases treated with theelin and glycine.

2. The dosage and chemistry of the substance, glycine, has been reviewed.

3. The therapeutic effects of other glandular products and other drugs are recorded.

CONCLUSIONS

1. The dosage of glycine is by no means determined. Glycine is not toxic when given in fairly large amounts over long periods of time. There appears to be no advantage to the intravenous administration of glycine.

2. Metabolic studies of creatine and creatinine in cases of muscular dystrophy are of value in the diagnosis and the study of clinical improvement.

3. Glycine administered in fourteen cases of pseudohypertrophic muscular dystrophy over long periods of time showed no striking therapeutic effects.

4. Glycine administration may stop the progress of the disease in muscle fibers not already atrophied or fibrosed.

5. Glycine may be of definite benefit in early cases, but it is of little value in the advanced type of case.

6. Its use in the early cases of muscular dystrophy is to be encouraged.

7. Our opinion now is that something else is needed along with glycine to create a storage of creatine in the muscle tissue. This substance may be exogenous or endogenous, or a combination of both.

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614 HUME MANSUR BUILDING

Pediatric Clinics

THE DEPARTMENT OF PEDIATRICS, UNIVERSITY OF MINNESOTA

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LIKE most other university departments of pediatrics in America, that at the University of Minnesota is comparatively young. Although regular lectures on the diseases of childhood were given under the auspices of the Department of Medicine as early as 1895 by Doctor J. T. Christison, an active member of the present pediatric staff, it was not until 1915 that the Department of Pediatrics was organized as a separate and independent unit. Under the able direction of its first chief, the late Julius P. Sedgwick, however, it soon became one of the most popular and productive departments in the Medical School. With a few minor interruptions its development has continued at a steady pace since that time, and the value of its influence on the practice of pediatrics in the Twin Cities and the Northwest generally can hardly be overestimated.

Following the death of Dr. Sedgwick in 1923, Prof. Clemens von Pirquet was brought from Vienna to head the department, but, after a few months of service, he resigned to return to his former position. The vacancy left by his resignation was filled by Dr. F. W. Schlutz, who served as professor and head of the department from 1924 to 1930. Since the latter date the author has occupied this position.

ORGANIZATION AND STAFF

The department is now organized on the so-called Harvard full-time plan, that is, the head of the department and a few full-time assistants are employed on a salary basis. In addition the chief is allowed to care for a limited number of private patients or to see patients in consultation with other members of the profession. His time and that of other members of the full-time staff is devoted almost exclusively, however, to the care of indigent hospital patients, to teaching, and to research. In addition to the full-time staff there is a larger part-time staff composed chiefly of practicing pediatricians who teach without salary.

At the present time the full-time staff consists of one professor, one half-time associate professor, two assistant professors, two instructors, four clinical fellows (or residents), two research fellows, one part-time research fellow, one secretary, four "straight pediatrics" internes and four rotating internes. The part-time staff consists of six associate professors, six assistant professors, fourteen instructors, and eight assistants. One of the part-time instructors is a dentist, who specializes in children's dentistry.

CLINICAL AND LABORATORY FACILITIES

Practically all of the pediatric hospital services of the Twin Cities are directly or indirectly in charge of members of the pediatric staff of the University and so are available for teaching purposes. All the regular teaching is carried on, however, at the University Hospital and at the city hospitals of Minneapolis and Saint Paul.

The Minneapolis General Hospital, which is situated approximately one mile from the University, has a total of 146 beds for children, exclusive of the nursery for the newborn. Visits to the out-patient department total approximately 16,000 per year. Half of the junior bedside work and half of the senior case teaching in pediatrics are conducted at this institution. Dr. E. J. Huenekens, associate professor of pediatrics, is chief of the children's service. The Ancker Hospital in Saint Paul, which is situated about seven miles from the University, has a similarly organized service with approximately one-third the amount of clinical pediatric material available for teaching. Half of the junior students receive their bedside instruction in the contagious and noncontagious diseases of childhood in this service. Dr. Walter Ramsey, associate professor of pediatrics, is chief of the pediatric staff.

The Infant Welfare Society of Minneapolis, under the direction of Dr. E. J. Huenekens, has generously made its clinics available to the Department of Pediatrics of the University for teaching well-baby care. Two such clinics are held weekly in the university out-patient department. In addition, the Department of Pediatrics has direct charge of the infants in the Saint Paul Salvation Army Home for illegitimate babies. The full-time pediatric staff has recently assumed responsibility for supervision of the purely medical care of patients at the Shriners' Hospital for Crippled Children, which is situated less than two miles from the University.

In 1923 the University of Minnesota received a gift of $1,000,000 from Mr. William Henry Eustis "for the medical and surgical care of needy crippled children." Supplementary additions to the original gift had brought the total endowment to nearly $2,000,000 at the time of the donor's death in 1928. Earnings have now brought the total value of the gift to approximately two and one-half millions of dollars, exclusive of the Eustis division of the University Hospital, which was constructed between the years 1928 and 1930 at a cost of approximately $250,000. For the sake of economy in construction and maintenance, this unit with its six floors was built as an addition to the University Hospital proper. At some future time a convalescent home is to be built out of earnings from the endowment on a 44-acre tract of wooded land overlooking the beautiful Mississippi River gorge approximately two miles from the University Hospital.

The new Eustis wing houses all children admitted to the University Hospital and is the center of all pediatric activities. The first floor is occupied by chemical research laboratories, orthopedic brace shop, the hospital record room, a teaching amphitheater with seating capacity of two hundred, and a complete physiotherapy division, including a swimming pool. The pediatric offices, a resident staff laboratory for routine and research work, a small seminar room, an out-patient nutrition clinic room, a special cast room, and separate out-patient quarters for infants and older children occupy the second or ground floor. The third floor houses the isolation and contagious disease patients (twenty beds and two Drinker respirators), a small library for patients, and the social service department of the Hospital. Practically all of the fourth floor is occupied by the children's orthopedic service with twenty-two beds and a complete operating suit. On the fifth and sixth floors there are fifty beds for noncontagious medical and general surgical pediatric patients above the age of infancy, a small metabolism ward for several patients, a well-isolated nursery with thirty cribs for newborn, a room for premature infants, completely equipped with automatic air-conditioning devices for both summer and winter control, a twenty-four-bed wing for sick infants, and a central milk laboratory to serve all infants who receive artificial feedings. In addition to the general out-patient clinic, which operates in the forenoon only, special clinics are held in the afternoon periods. The most completely organized are those for well-baby care,

heart disease, allergy, speech disturbances, and the diseases of metabolism. The total visits to the pediatric out-patient division at the University Hospital amount to approximately nine thousand annually.

The various service departments of the University Hospital proper, such as x-ray, social service, clinical laboratories, physiotherapy, and pharmacy, are located in such close proximity to the pediatric wing as to make duplication of these by the department of pediatrics unnecessary.

The pediatric staff and students have easy access to the University Library, which ranks high among American medical libraries for its collection of bound and current periodicals. A combined departmental and personal library containing fifteen current periodicals and a fair assortment of textbooks and pediatric systems is maintained for added convenience. The department maintains a series of well-equipped laboratories for special research, chiefly along chemical, hematologic and bacteriologic lines. Some of these are housed in the Eustis Hospital Building and others in the nearby Medical Science Building.

RELATION TO OTHER DEPARTMENTS

At the University Hospital the Department of Pediatrics is responsible for the admission, general supervision, and medical treatment of all children under the age of sixteen years. Greatly to the credit of Dr. J. C. Litzenberg, professor of obstetrics and gynecology, and Dr. Sedgwick, the University of Minnesota Hospital was the first institution in America and the second, if not indeed the first, in the world to adopt the plan of transferring the responsibility for the care of the newborn from the obstetric to the pediatric service immediately after birth. Adopted in 1913, this policy has continued to date with entire satisfaction to both departments. A representative of the pediatric service is notified whenever an obstetric delivery takes place in order that he may examine and care for the infant immediately. In any case in which difficult labor or other complications are anticipated, special preparations for emergency treatment of the infant are made by the pediatrician, leaving members of the obstetrical staff free to devote their attention entirely to the mother. In determining the advisability or inadvisability of breast feeding in any but the routine uncomplicated cases, representatives of the two departments again confer in order that the welfare of both mother and infant can be adequately considered. Before the mother and her infant are discharged, the baby is completely examined and the mother is given detailed instructions regarding its future care by a member of the pediatric staff.

All major operations and surgical after-care are the responsibility of the Department of Surgery, excepting those pertaining to the eye, ear, nose and throat which are carried out under the independent Department of Ophthalmology and Otolaryngology. While the patient is usually transferred to the other service before operation, his medical care remains a pediatric responsibility. Most of the borderline diagnostic and therapeutic procedures, such as blood transfusions, aspirations, encephalography, and the treatment of burns, are carried out on the pediatric service. The resident members of the pediatric staff now perform all autopsies on children under supervision of the hospital pathologist. Where there is overlapping of clinical problems, as in cases of acute abdominal disease or suspected brain tumor, a representative of the surgical staff is called by the pediatrician as soon as the patient is admitted in order that the responsibility for the diagnosis and treatment can be shared by the two departments to the patient's advantage. Due very largely to the generous attitude of the entire personnel on the associated services, this plan of interdepartmental cooperation works very smoothly for all concerned.

The Department of Pediatrics maintains a fairly close relationship with the Institute of Child Welfare, which was organized at the University in 1925 chiefly for the purpose of studying all phases of growth and development in normal children. It was set up as a project to be carried out during a period of thirteen years. Its maintenance has been assured by a generous grant from the Laura Shellman Rockefeller Foundation. With a nursery school for thirty-six children between the ages of two and five years, an experimental kindergarten for fifty half-day pupils, a parents' consultation service, and an excellent staff, it offers exceptional opportunities for those interested in the problems of normal growth and development. The staff consists of its able director, Prof. John E. Anderson, three additional full professors, who are especially well trained in psychology and child welfare work generally, one assistant professor, one half-time associate professor, three full-time instructors, and three part-time pediatricians. There is an exchange of lectures between the two departments, and members of the institute staff are called in consultation on pediatric cases where psychologic studies are required. The extensive research program of the Institute has had the cooperation of various members of the pediatric staff from its beginning.

The Division of Pediatrics of the Mayo Foundation for Medical Education and Research at Rochester is part of the Graduate School of the University of Minnesota. The relationship between it and the Department of Pediatrics in the Medical School is most cordial, and cooperation in teaching and other academic activities is as close as the distance separating the two departments will permit.

TEACHING AND RESEARCH

All required undergraduate work in pediatrics is given in the third and fourth years of the regular medical course. The junior student receives sixty-six one-hour amphitheater lectures or demonstration clinics and in addition has the equivalent of eighteen one-hour periods of bedside teaching in the contagious and a like number of periods in the noncontagious diseases of childhood. The senior student has thirty-three one-hour amphitheater clinics, which are held weekly throughout the year, in addition to the six or seven weeks which he devotes exclusively to pediatrics from 9 A.M. to 6 P.M. daily. In addition to his regular case work with hospital patients, besides rounds and general dispensary experience, the clinical clerk is assigned to the special pediatric clinics on speech disturbances, cardiac disease, allergic disorders, metabolic and endocrine disorders, and well-baby care. Special lectures are given by university faculty members, who are not on the pediatric staff, as follows: six by Dean R. E. Scammon on physical growth and development; two by Dr. John E. Anderson, director of the Institute of Child Welfare, on psychologic development; two by Dr. Bryng Bryngelson of the Department of Speech on speech defects; one by Dr. E. T. Bell, professor of pathology, on the clinical pathology of the kidneys; one by Dr. Henry F. Helmholz, chief of the pediatric section of the Mayo Clinic, on infections of the urinary tract; and one by Dr. Samuel Amberg, chief assistant to Dr. Helmholz, on diseases of the liver and biliary tract in children. These illustrated lectures constitute a part of the sixty-six-hour amphitheater course given in the junior year. Some elective courses also are offered to qualified junior students. Regular lecture courses are given semiannually to the pupil nurses by the pediatric staff.

Graduate teaching in the various branches of medicine, pediatrics included, has long been made a special feature at the University of Minnesota. The majority of full-time staff members between the ranks of interneship and assistant professorship are registered for both major and minor graduate courses and a fair-sized minority of those so registered earn either the M.S. or the Ph.D. degree after from two to four years of postgraduate study. In addition to his major clinical work in

pediatrics, a fellow or instructor must present a thesis or original research and must complete certain minor courses in the fundamental or preclinical sciences before he is eligible to come up for a final examination. While only the scholarly type of man is encouraged to pursue special investigations, the influence of regular graduate study appears to be beneficial even for the man who expects to spend his entire career in practice alone.

In addition to the regular clinicopathologic conferences and history meetings held weekly, the full-time staff members hold a weekly seminar for review of fundamental topics bearing on pediatrics and a joint x-ray conference with the Department of Radiology for a review of all current x-ray films. Clinical clerks on the pediatric service are required to attend the latter. The general pediatric staff has one evening program bimonthly for presentation of scientific and clinical papers by either staff members or guest speakers. At least twice yearly the full-time pediatric staff of the Mayo Clinic and that of the Medical School meet at Rochester or Minneapolis for joint clinical rounds and presentation of an informal scientific program based on original work. Practically all members of the permanent full-time staff and some of the part-time members devote a fair share of their time to medical research. The major portion of the problems under investigation are of a fundamental character although practically all have originated at the bedside. As examples of the types of original studies being made at the present time, the following may be listed: further studies on the relationship of lipid metabolism to immunologic processes and a search for factors which might alter the various fractions of the blood lipids independently; study of the convulsive mechanism in parathyroid tetany in relationship to water and mineral metabolism; determination of the specific relationship of certain inorganic ions, particularly Na, K, and Cl to blood pressure and to carbohydrate metabolism in diabetic children; comparative chemical analyses of normal and epileptic brains; a study of enuresis from the genetic viewpoint; relationship of state of hydration to resistance to infection; water and mineral balances in diabetes insipidus and in certain forms of edema; a study on infantile eczema from the point of view of the unsaturated fatty acid metabolism; phosphatase activity and mineral metabolism in osteogenesis imperfecta; study of childhood tuberculosis from the standpoint of native resistance, allergy, and acquired immunity; determination of the antirachitic potency of ergosterol activated by the electrodeless discharge process.

Critical Review

SURGICAL PEDIATRICS

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IT IS interesting to note the increased frequency of reference in recent literature to the subject of surgical pediatrics. Whether this foreshadows an additional division of surgery or the beginning of segregations within the specialty of pediatrics is impossible to estimate. Certain it is that a knowledge of the peculiar reactions, the active physiologic processes, and the anatomic limitations of infancy and childhood must be so thorough and fundamental that the pediatric surgeon must be possessed of a pediatric as well as a surgical and an aseptic conscience. The differences between adults and children are not alone matters of size but are even more marked in anatomy, physiology, and psychology.[1, 2] These differences have given rise to the specialty of pediatrics, and the same facts and conditions are equally important when applied to surgery. Since the limits of safety are narrow in the surgery of children and even narrower in that of infants, surgical procedures and technic must be varied accordingly. The statement that children do not stand surgery well is being much less frequently heard as the realization is becoming more general that they do not stand *adult* surgery well.

In an excellent article Schulz[3] says, "Infants and children present surgical problems so different from adults that the practice of pediatric surgery probably should be as specialized as is the practice of pediatries." And later, "The field of pediatric surgery is important and large enough to deserve some place in the curriculum of medical education." With the opinion, however, that all possible surgery should be deferred until after the age of eighteen or twenty-four months and operating upon an infant only for emergencies or conditions incompatible with life, we cannot agree, and would refer to an earlier statement in the same article to the effect that infants and children can easily undergo major surgery if the physiologic mechanism is understood and if there is good preoperative and postoperative care and good operating. In the congenital defects involving muscle function, normal anatomic relations should be secured as soon as possible so that normal growth and development may take place during the early months of life when physiologic processes are in the period of greatest activity.

The statement regarding medical curriculums deserves more than passing mention. How often does a young man leave a medical school and a general interneship with full knowledge and ability to do a gastroenterostomy or a hysterectomy only to find himself confronted during his early years of practice by problems in the surgery of infants or small children which he is totally unprepared to meet. If he

has had no instruction in the preoperative and postoperative requirements of these little patients and no warning of the operative hazards, the unnecessary fatalities which must inevitably occur are chargeable not to the young man but squarely to the faculty of his school in whom he had placed his trust.

In a masterly article Prof. John Fraser of Edinburgh reviews the progress of pediatric surgery during the past twenty-five years.[4] A review of such a review is impossible. It must be read to appreciate the great breadth of experience and vision and the delightful style. He summarizes the advancements of the quarter century as, (1) striving for simplicity, (2) application of physiologic and anatomic principles to the treatment of disease, and (3) endeavoring to attain the objective with the least possible disturbance of the processes of body chemistry. A thesis could be written on each of these.

The utilization of the principles of rest and minimum interference with the physiologic defense mechanism[5] is seen in many of the methods of treatment of infection which are perhaps considered of recent origin but which may well be a revival of Hilton's principles of rest enunciated nearly a century ago. As such may be mentioned the Orr treatment of osteomyelitis, the saline pack, the Carrel-Dakin method, the phenomenon of bacteriophage, vaseline packs in chronic sinuses or fistulas[6] using irradiated vaseline which gives off no ultraviolet emanations, etc. The principles may well be applied to the care of very sick infants and children who are often in a narrow and unstable zone between recovery and death. Meddlesome therapeutics or too close adherence to a disturbing nursing routine of external cleanliness may push such a patient over the wrong boundary of the zone rather than assist him over the right one.

ANESTHESIA

While ether is undoubtedly the safest anesthetic for general use, the avoidance of psychic shock with consequent endocrine disturbance and postoperative upset in cases requiring multiple anesthetics deserves careful consideration.

To meet this condition there is an increasing popularity of basal anesthetics, chief among which are avertin and the various barbiturates. Evipan,[7] a barbiturate used intravenously, gives a quick anesthesia of comparatively short duration. It has the same depressant effect on respiration and blood pressure that has been noted in connection with the use of other barbiturates. This may at times require an airway or stimulation by carbogen, but untoward results are extremely rare, especially when a skilled anesthetist and careful postoperative nursing are available. If preoperative narcotics are used, total anesthesia is possible,[8] but the risk is increased; the greatest field of usefulness is as a basal anesthetic supplemented by light inhalation anesthesia. Tables of dosage are supplied by the manufacturers and should be followed exactly.

Coramine[9] is of great value as an antidote for either avertin or spinal anesthetics and may be given intravenously for quick effect or intramuscularly or orally when more prolonged action is desired.

Spinal anesthesia is of limited value in children, but caudal anesthesia has a distinct field of usefulness for urologic procedures, permitting valuable diagnostic measures in pyuria and enuresis and making urethral surgery possible without general anesthesia.

Ethylene is a valuable anesthetic agent, the use of which has been unnecessarily limited by undue emphasis upon the hazard of explosion.[11] It is most satisfactory when used with the same skill and care which should be exercised in the administration of any anesthetic. Moist climates tend to eliminate the danger of static, and a few simple precautions reduce it to a minimum. More explosions have occurred from gas-oxygen-ether anesthesia than from ethylene, and in one series 27,000 ethylene anesthetics have been given without accident.

The outstanding objection which has been raised to intravenous and rectal basal anesthetics is the impossibility of stopping absorption at any given time or stage, as is possible with inhalation anesthetics. This objection of course deserves careful consideration, but it can be met in practically all instances by foresight and preparation for possible emergencies, as should be the practice when using any anesthetic. The type of anesthetic to be used should be suited to the individual case and will depend upon the temperament of the child, the pathologic condition, the necessary surgical procedure, and the experience of the anesthetist. The skill of the anesthetist lies not only in his ability to administer an anesthetic but also in his ability to choose the best one for the patient.

Sudden death during the induction of anesthesia of any type may occur and has usually been considered as due to idiosyncrasy or, in children, to some vague thymic abnormality. Idiosyncrasy suggests sensitization which in turn suggests allergy, and a most interesting study[12] correlates these conditions with so-called "thymic death." The pathologic changes in such instances are almost identical with those found in cases of known anaphylactic shock, and the assumption is that such shock is not necessarily dependent upon a protein antigen but may be produced by a nonprotein substance absorbed through the respiratory tract. Such allergic shock, violent enough in some instances to cause death, will occur if there is a condition of extreme sensitivity with rapid absorption of an amount of antigen definitely above the individual tolerance. In many of the cases studied there was a family history of allergy of some kind, and in a series of thirty children showing enlarged thymus by x-ray twenty-four had an allergic history or positive dermal tests.[13] The usual tests have proved unreliable for nonprotein anesthetic agents, and the very pertinent suggestion is made that with allergic patients or those having allergic relatives small amounts of inhalation or local anesthetic be cautiously administered with a protective dose of ephedrine or epinephrine ready for immediate use.

The relation of an enlarged thymus to the allergic state has not been determined, but it seems probable that it is more intimate than the relation to the so-called obstructive thymic syndrome of stridor, cyanosis, cough, etc. In a series of 322 newborn infants with x-ray evidence of thymic enlargement, only fifteen showed clinical symptoms referable to this condition.[14]

ORTHOPEDICS

The merits of the operative and nonoperative treatment of joint tuberculosis has been argued pro and con for many years, the weight of opinion for some time having been in favor of nonoperative treatment in the average case in a child, largely on account of the time and employment factors. In recent literature, however, there is a constantly

increasing trend toward the advocacy of joint fusion by operation in children as well as adults. There should be no conflict between the two types of treatment, as surgery is simply a step in the entire course of treatment,[15] and should be used at the appropriate time. Since joint involvement is usually considered as a local manifestation of a general condition, the disease process must be treated as a whole, with the closest cooperation between the surgeon and the internist.[16] Only by such treatment can the patient be returned to the best possible condition in the shortest possible time.

The decision to use surgery and when to use it must depend upon the climate, the efficiency of medical treatment, and the quality of surgical skill available. When an adequate operation is performed in a case which has had proper preoperative care and the postoperative period of rest and protection well supervised, the prognosis for tuberculosis of the spine is surprisingly good.[17] The results in children, even when the time of choice for the operation is before five years of age, are excellent and after recovery these patients have participated in athletics or have done hard manual labor. Surgery should not be undertaken early in the average case, as it does not stop the disease process,[18] but it is to be used after the active progress of the disease has been controlled by the preliminary medical treatment and before weight-bearing has placed such a strain upon the lesion as to produce or increase a deformity. The entire course of treatment may require from three to five years.

The same combination of medical and surgical treatment is proving successful in treatment of tuberculosis of the weight-bearing joints, particularly the hip, the results being a marked reduction in the length of hospitalization and in the percentage of recurrence. The details of treatment vary, and when there is extensive bony involvement, the results are not as good as in less advanced cases[19] but the rational use of surgery is being advocated even by some who have formerly been strongly in favor of nonoperative treatment.[20]

The diagnosis of congenital dislocation of the hip should be made early if reduction is to be accomplished in the simplest and most satisfactory manner. The condition is usually discovered after the child has begun to walk, perhaps in the first half of the second year, at which time the mother seeks medical advice on account of a limp. The condition is painless and often is ascribed to an exaggeration of the toddling gait until its persistence causes comment. The recognition of the defect should be a responsibility of the medical profession rather than of the parents or neighbors. An examination soon after birth in most cases and always well within the first six months will either permit a definite diagnosis or show sufficient abnormality to indicate a roentgenogram. Even in the newborn the suggestive signs are an asymmetry of the gluteal creases and the skin folds on the inner surfaces of the thighs, external rotation of the affected thigh when in a position of rest, limitation of abduction, and shortening of the thigh shown best with the knees flexed.[21] If treatment is begun during the first six months, secondary changes in the capsule and in the position of the head of the femur having not yet developed, reduction is usually easily accomplished, often without the necessity of an anesthetic.

In the treatment of congenital clubfoot, it cannot be too emphatically stated that correction must be begun during the first days of

life and carried on persistently and vigorously until marked overcorrection is obtained. Particular attention is necessary regarding the correction of the equinus position of the os calcis[22] to avoid the production of a "rocker foot" in which the correction is mainly in the forefoot, leaving the position of the posterior portion practically unchanged. Lateral roentgenograms may be necessary but in infants are often difficult to interpret. Comparison with a normal foot should be made. Lack of correction of this portion of the foot is responsible for many unsatisfactory results and so-called relapses.[23] When the condition is permitted to persist into early childhood, it often becomes so resistant that manipulative correction is impossible and extensive resection of the ligaments and capsule is necessary to permit rotation of the tarsal bones into correct position. The removal of portions of the tarsus is inadvisable before early adult life on account of interference with growth and development. After a position of overcorrection is obtained, persistent and thorough supervision is necessary, often involving periods in plaster and special attention to corrective shoes during the developmental years of childhood if recurrence is to be avoided and the best ultimate result obtained.

The relation of generalized osteitis fibrosa, or von Recklinghausen's disease, to parathyroid hyperplasia or tumor is gradually emerging from the present wave of endocrine enthusiasm as a fairly fixed and stable conception. It is to be borne in mind, however, that skeletal changes occur in dysfunction of the thyroid, pituitary, pancreas, and suprarenals as well as that of the parathyroids[24] and that the surgical aspects of many osteomalacic diseases[25] have not been determined, therefore it is particularly essential that indications be clear and definite before parathyroid surgery is recommended. Among the general symptoms[26] may be mentioned, nausea, vomiting, cramps, muscular hypotonia, thirst, altered renal functions and bone pains. There are often fractures and deformities of the long bones due to cysts or tumor formation, and calculi and lime deposits may occur in the kidneys, lungs, stomach, and myocardium. A tumor in the neck is rarely palpable in children. The blood picture of high calcium and low phosphorus is characteristic, and the urinary calcium on ordinary diet is six or eight times the normal. The skeletal changes as shown by roentgenography are never localized but are general and should be controlled by comparison with a similar study of a normal child of the same age. Surgery is complicated by the possible existence of aberrant parathyroids, the advisability of preserving a sufficient amount of functioning gland tissue, and the lack of relationship between the size of the gland or tumor and the symptoms. Close postoperative supervision is necessary on account of the possibility of the occurrence of tetany; calcium or parathyroid substitution therapy may be required. The differential diagnosis and treatment are difficult, but in suitable cases the results are satisfactory and the prognosis good.

In the early stages of infantile paralysis, rest is the greatest factor in recovery.[27] This is the stage of cell inflammation and damage during which the cells should be protected by reducing nerve impulses to a minimum.[28] There should be no manipulation or irritation. The daily nursing care should be conducted in the gentlest possible manner and confined to absolute essentials. The affected muscle groups should be relieved of tension, postural protection by a plaster of Paris

shell being preferable to splints. After the disappearance of muscle tenderness, which may take six or eight weeks, light massage, muscle training, and exercise of the affected muscle groups in warm water may be cautiously begun. It is particularly important that the patient, the family, and friends be specifically instructed at this stage that the ideas and methods of athletic training are particularly disastrous and that overexercise or the slightest fatigue does not build up muscle power but causes actual weakening and delays recovery. Continued support, avoidance of strain and stretching of affected muscles, and carefully supervised, graduated exercises are essential during this stage. When a warm pool is available exercises with water support are most beneficial.

Fractures of the arm are comparatively frequent in children and those involving the elbow joint are particularly prone to result in more or less serious disturbance of function. The position of acute flexion following reduction is deservedly popular, but little stress has been placed upon the accompanying pronation or supination of the forearm. Failure to obtain a normal carrying angle is usually due to the use of the flexion-supination position instead of flexion-pronation.[29] Late or poor reduction causes excessive callus formation, and acceleration of development in ossification centers or other epiphyseal disturbance[30] with resultant malfunction. In condylar fractures, manipulation and closed reduction is difficult and uncertain. Early or immediate open reduction with wire nail fixation, if necessary, gives a high percentage of excellent results. In fracture of the neck of the radius, manipulation rarely effects satisfactory reduction.[31] Open reduction permits accurate replacement of fragments and of the epiphysis. Resection of the head is rarely necessary in children and results in an unstable elbow with an increase of the carrying angle. In these fractures there is often no crepitus, and a sign which is occasionally valuable is a referred pain at the lower end of the radius when pressure is made over the head.

The idea that skeletal traction in children is contraindicated because of danger of osteomyelitis or injury to epiphyseal lines deserves little consideration when modern aseptic technic and the Kirschner wire type of traction are used.[32] This method should not be used routinely nor in all cases, but it is valuable where there are multiple fractures, tender, or injured skin surfaces, malunion, or delayed reduction.

The Orr treatment of osteomyelitis has received wide publicity during recent years and has proved one of the outstanding contributions to the care of this disabling and refractory disease. As is always true with any departure from the usual in the practice of medicine, this method has been subjected to a most searching scrutiny and analysis by the profession. One study[33] would indicate that the success of the method depends upon the development of a bacteriophage. After careful preparation of the osteomyelitic cavity, packing and immobilization, the appropriate bacteriophage is introduced through an indwelling tube, the application being repeated once or twice weekly without disturbing the packing. An autogenous bacteriophage as well as polyvalent stock preparations may be necessary to combat resistant strains of bacteria. The cast is removed and dressings changed every two months; in most cases healing takes place in about eight months. About 3 per cent of the cases resist the bacteriophage treatment. Vaseline of varying consistency instead of vaseline gauze is used for

packing various types of cavities. The use of irradiated vaseline has given no better results than the use of the plain. Mention is made of the use of bacteriophage superficially in cellulitis and intravenously in staphylococcic septicemia. The hemolytic staphylococcus is particularly suspectible to bacteriophage therapy.[34, 35] In this connection it will be interesting to follow the development of the use of nutrient peptone broth as a local application[36] and by interstitial injection[37] to stimulate the reticuloendothelial system[38] and the use of irradiated blood[39] by autotransfusion in staphylococcic septicemia.[40]

The success of the maggot treatment of osteomyelitis has led to a similar critical analysis[41] for the purpose of eliminating the obviously disagreeable features while retaining the beneficial ones. It was discovered that products of maggot activity stimulate the reticuloendothelial system and inactivate the leucocidin produced by the bacteria. This action is duplicated by the use of 0.25 per cent pieric acid in 8 per cent glycerine, which inactivates the bacterial toxin, and by an aqueous suspension of calcium carbonate, which is a powerful stimulant of the local physiologic protective mechanism. Applications are made daily or on alternate days, and rapid improvement is reported with complete cure in from one to six months. The usual surgical treatment is of course necessary.

The stimulation of the defense mechanism by a specific toxoid[42] in cases of osteomyelitis and local infections due to the staphylococcus has received a considerable amount of favorable notice. As yet, however, the production of the toxoid is somewhat limited and a critical estimate of its value must be withheld until more reports are available.

BURNS

The use of 10 per cent tannic acid in the early treatment of burns[43] instead of the 5 per cent solution formerly recommended is said to eliminate the necessity of excision of burned tissue. The stronger solution penetrates and coagulates down to sound tissues better and more rapidly than the weaker. Epithelialization does not take place under the coagulum in third degree burns, and skin grafting should be used as soon as the general condition will permit, especially on the flexor surfaces of joints. All general supportive and restorative measures should be used and in severe cases special nursing care is essential.

Some question has been raised as to the possibility of deep necrosis from the pressure of the hard coagulum produced by tannic acid[44] and the substitution of a 1 per cent aqueous solution of gentian violet recommended. Reports of this treatment seem favorable.[45] It is claimed that the dye is specific for gram-positive bacteria and, in addition to its greater antiseptic value, has no effect on living cells. It forms a firm, dry, adherent but pliable covering and is analgesic. On account of the lack of toxicity there is no danger of using too much. The method of use and protection for the eyes are the same as for tannic acid, and the same rules are to be observed regarding maceration and removal of the coagulum preparatory to skin grafting. The results as regards epithelialization seem to be similar to those obtained by the tannic acid treatment. The method on the whole presents some slight refinements over the tannic acid treatment, but the most radical difference would appear to be a matter of color.

INTRACRANIAL CONDITIONS

Successful treatment of intracranial tumors is so dependent upon early diagnosis that possible early symptoms should be constantly in the minds of those who come in contact with children. Prominent among these are persistent vomiting and headache.[46] The child often shows a change of disposition becoming listless, drowsy, or irritable. Disturbances of equilibrium and vision are usually later symptoms although changes in the fundus of the eye occur early in certain tumors. The persistence of any symptoms which may indicate an intracranial tumor should be the signal for a careful ophthalmoscopic and spinal pressure study followed by a thorough neurologic examination including ventriculography if indicated. The possibility of multiple tumors[47] should be borne in mind if the neurologic findings seem confused, for the condition, although rare, has been reported. The more common use of the ophthalmoscope[48] will aid in bringing cases to the neurosurgeon at a stage when prognosis is more hopeful.

Ventriculographic interpretation has been somewhat clarified by a study[49] in which the ventriculograms are correlated with an accurate cast of the ventricular system, and as a result an improvement has been made in the terminology used. The clinician should be present when a ventriculogram is taken as posture is extremely important and suggestions as to the possible location and type of the lesion will enable the roentgenologist to obtain more accurate findings.

The use of thorotrast in the demonstration of vascular abnormalities in the brain[50] or elsewhere[51] is interesting and is reported to be free from untoward results. The use of a radioopaque liquid medium in the rapidly moving blood stream, however, requires such a specialized technic if results are to be at all dependable that its use will be much restricted for some time to come.

CERVICAL CONDITIONS

Branchial and thyroglossal cysts[52] should not be mistaken for cervical abscesses and incised. Secondary infection results and renders later excision difficult. These cysts are usually smooth, semifixed but not indurated, moderately tense, and painless. They are not tender unless secondarily infected or pressing upon adjacent nerves. Branchial cysts lie at the anterior border of the sternomastoid muscle and thyroglossal cysts in the midline. Fistulas and sinuses derived from the same embryonic structures open externally in the same locations in the great majority of cases, although internal openings occasionally occur.[53] Before secondary infection, the discharge from these sinuses is a clear mucoid or a thin milky fluid and rarely profuse, the complaint being the embarrassment caused by its appearance rather than discomfort. Upon palpation, a cord can be felt passing upward and inward toward the throat, accentuated by traction upon the skin at the fistulous orifice. Thyroglossal sinuses pass through the substance of the hyoid bone, and branchial ones lie in close contact with the vagus nerve and great vessels. Cartilage may be present at some point along the tract or even occur as an isolated cartilaginous tumor,[54] in which later instance removal is optional as such tumors are painless and malignancy does not develop.

The removal of branchial and thyroglossal cysts and sinuses requires thorough and careful dissection with attention to vagus symptoms, such as cough and irregularity of the pulse. The excision must be complete or troublesome recurrences follow.

Other lateral tumors in the neck[55] are, cervical glands, dermoids, aneurysm, hygroma, and very rarely thyroid, parathyroid or carotid body tumors. The only midline tumor which may require differentiation is a sebaceous cyst. Cystic hygroma may be difficult to differentiate from branchial cyst but usually has a much more rapid growth and lies posterior to the sternomastoid muscle. If surgery is contraindicated and pressure symptoms require relief injection with a selerosing solution of 5 per cent sodium morrhuate[56] may prove successful. If at all possible, however, excision is the preferable treatment because of the necessity for complete removal of the secreting surface and the possibility of an undesirable irritating effect of the selerosing solution upon adjacent structures.

The surgical removal of tuberculous cervical glands[57] should be reserved for early selected cases in which the process is well localized and the general condition good. All antituberculosis measures should be used both before and after excision. Such treatment is a definite and direct method of removing a focus which may become active at a later date. In carefully selected cases, results are 90 per cent satisfactory. For the treatment of more advanced cases, either with or without sinus formation, x-ray treatment as an adjunct to general measures is of value.[58]

The careful and thorough use of general antituberculosis measures will still remain the fundamentally sound and necessary treatment of tuberculosis in whatever part of the body it may occur. Surgery and local measures to improve physiologic defense and resistance should be used whenever indicated, but under no circumstances should they be considered as major factors in treatment, or allowed to overshadow the general regimen.

Theories as to the cause of congenital torticollis have often placed the responsibility upon muscle rupture or hemorrhage due to birth trauma or upon some congenital defect in enervation or blood supply. A recent study[59] suggests that it is caused by venous obstruction and constriction in the sternomastoid muscle of one or two hours' duration during labor. The constriction causes intravascular clotting with resultant localized fibrosis. The fibrotic tumor prevents normal growth of the muscle with relative shortening, and the development of increasing torticollis. Early surgery before secondary deformities occur is indicated.

Thyroid disorders are seen fairly frequently in children,[60] particularly in those sections of the country which lie in the "goiter belt." Both congenital goiter and congenital cretinism occur. Colloid goiter in general does not need surgery and may be benefited by iodine. Toxic goiter should be treated surgically if it is so large as to cause pressure symptoms or if it does not respond to medical treatment. Adolescent goiter is not a serious condition, and usually there is a normal basal metabolic rate. Exophthalmic goiter in children under ten years of age[61] occurs in girls in about 95 per cent of cases. Surgery is seldom indicated, but the medical treatment is prolonged and exacting. Focal and general infections appear to have an etiologic

significance and should be thoroughly treated. Toxic foci, however, should not be removed during the height of the syndrome, because of toxic shock and the danger of hemorrhage due to disturbed calcium metabolism.

NEUROLOGIC CONDITIONS

An operative treatment of spina bifida which gives a mortality of only 5 per cent in a series of sixty cases is well worth reporting.[62] If there is no leakage of spinal fluid, the operation is performed as soon as the infant has regained its birth weight, but if there is drainage, as soon as the sinus is closed; the reason for early operation being that 80 per cent of these children die during the first year if operation is not performed. Most of the sac is saved because of easier closure and minimal disturbance of nerve roots, not because of any absorptive characteristics of the sac. Frequent preoperative tapping, sudden release or change of pressure, and infection stimulate secretion. The tumor should not be permitted to increase greatly in size. Postoperative hydrocephalus begins before the operation or is due to infection rather than to failure to carry out careful postural treatment after operation. Paralysis is not a contraindication to surgery, as careful freeing of the nerves will allow improvement in function which may become very good. Neither is a broad base with wide bony defect a surgical contraindication. Low postoperative mortality depends upon conservation of body heat and blood, prevention of rapid loss of spinal fluid, short, light anesthesia, and maintenance of nutrition.

One can but wonder at the success which is reported from widely varying methods of surgical treatment of this serious condition. It would seem that perhaps the fundamental principle of treatment or the true underlying physiopathologic condition has not yet been formulated. It is to be hoped that the procedures described will prove at least equally productive of good results as former ones, as the change will be in the interest of simplicity and reduction of hospitalization.

With the constantly increasing knowledge of the function of the sympathetic nervous system and the widening of the fields of application of that knowledge, possibilities of treatment are unfolding which permit relief of many conditions which formerly were of necessity endured or treated blindly, with varying degrees of poor results. The sympathetic nervous system controls and regulates the body functions and activities which are without the field of consciousness, and we take these functions for granted until some interference with the perfection of its control makes us acutely conscious that something is wrong. Aimless attempts at correction have often served only to aggravate conditions. This complex system with its cooperative antagonist, the parasympathetic system, is the great adjuster by virtue of which the body is able to withstand the manifold insults, both internal and external, to which it is constantly subjected. It regulates the temperature, controls the sensory thresholds, is the guardian of the various sphincters, controls the filling and emptying of innumerable cavities and containers, releases reserve stores and forces when emergencies arise, mobilizes defense mechanisms, and so on through an almost endless series of automatic activities. When it fails to function or functions erratically, trouble ensues. A few of its cells go wild and after two or three months of gastrointestinal disturbance, anemia, fever, and a rapidly developing abdominal tumor, an infant or small

child dies; the diagnosis is neuroblastoma of the adrenal or adjacent sympathetic ganglia.[63] The diagnosis is occasionally made by the presence of metastases in the membranous bones, but the prognosis is nearly 100 per cent fatal, and operation seems to hasten the end.

Hirschsprung's disease occurs when there is a disturbance of balance of the sympathetic system, the filling mechanism of the distal half of the colon being overactive. Sympathetic irritability or stimulation tightens the sphincter and exercises a brake action on colonic peristalsis with the resultant picture of hypertrophy and dilation of the distal colon, spasticity of the sphincter, and massive fecal accumulation. The results following section of the sympathetic nerves to the distal colon are proving most satisfactory.[64] The functional results are excellent in the great majority of cases and relapses are rare, the occasional unsatisfactory outcome being probably due to some unsevered, abnormally located nerve filaments. A rather puzzling observation is to the effect that although the functional improvement has been reported to be apparently permanent, no corresponding anatomic return to normal has occurred. As a diagnostic measure to determine the probable operative result, spinal anesthesia or injection of the lumbar sympathetic trunk may be used. The same procedure is of value for preoperative emptying of the colon. Section of the inferior mesenteric and presacral nerves instead of the lumbar sympathetic trunk eliminates any effect on the vasomotor control of the legs. In cases of long duration, a considerable amount of training may be necessary to establish normal habits of evacuation.

Contrary to former ideas the sympathetic system is capable of transmitting sensory impulses under certain conditions of interruption of somatic nerve supply.[65] The significance of this action is not yet fully apparent.

As is usual with a new procedure, sympathetectomy is being tried in a great variety of conditions, in some of which it is proving disappointing.[66] Its value in spastic paralysis, for which it was originally developed, is rather limited. In a normally intelligent child with moderate spasticity of the lower limbs, it relieves a certain amount of the tension and makes walking somewhat easier. There is a tendency, however, to lose the improvement after a few years. It is of little value in spasticity of the upper extremities. In chronic arthritis where pain rather than joint change is the major symptom, relief is often prompt and striking. Diagnostic injections will give a fairly accurate indication as to the amount of relief which may be expected from operation. Good results are reported in cases of Still's disease when the operation is performed fairly early.[69] Perhaps the most satisfactory and spectacular results in children are seen in the cold, cyanotic limbs of infantile paralysis. The color becomes pink almost immediately; the sensation of warmth and comfort is most gratifying; ulcers, infections, and incisions heal quickly, and there is even a slight improvement in bone growth. These results are most marked immediately after operation but are still excellent six years later.

INTESTINAL TRACT

Abdominal symptoms suggestive of appendicitis may be caused by a Meckel's diverticulum.[68] The pain is usually localized higher than the right lower quadrant and may even be in the right hypogastrium. In

2 per cent of the patients operated upon for appendicitis, the pathologic condition was found to be a Meckel's diverticulum, the appendix being normal. Contrary to the usual opinion, inflammation is not the most common cause of symptoms[68] arising from a Meckel's diverticulum; hemorrhage ranks first, with intussusception second, and inflammation, obstruction due to bands, volvulus, etc., third. Heterotopic mucosa is frequently present in these diverticula, gastric, jejunal, and pancreatic tissue having been found. Of these the gastric mucosa is responsible for hemorrhage since the glands secrete and the gastric regulatory mechanism is absent. Ulceration caused not by peptic digestion of the mucosa but by the action of the hydrochloric acid[70] does not occur in the heterotopic mucosa but in the ileac mucosa adjacent to it or at the neck of the diverticulum. Pain from the ulcer follows the taking of food. Bleeding may be chronic or sudden and profuse the blood being of the upper intestinal type rather than of the currant-jelly type of intussusception. Perforation is a serious complication, whether occurring from ulceration or from inflammation, as protective peritoneal adhesions do not occur as readily as in appendicitis; general peritonitis is the rule. When the existence of a Meckel's diverticulum seems reasonably probable, surgery is indicated.

Heterotopic gastric mucosa may occur in diverticula or enterogenous cysts other than Meckel's,[71] diverticula projecting from other parts of the intestine and cysts being located in the abdomen or mediastinum. The symptoms and signs of diverticula are similar to those of Meckel's. The cysts may be of sufficient size to cause pressure symptoms or to be seen in the roentgenogram. Ulceration may occur with subsequent hemorrhage, the symptoms being dependent upon the location of the cyst. Pain is variable in location and intensity but often is referred to the navel or right upper quadrant and associated with meals. The symptoms at times are suggestive of intussusception.

Factors causing intussusception in infants[72] are abrupt changes in diet, catharties, foreign bodies, and sudden disproportion in caliber of the small and large bowel, to which might be added disturbed balance of the visceral sympathetic nervous system.[4] A fortunate situation existing in Australia may well be emulated in other countries; there the medical profession has become intussusception-conscious with the result that late diagnosis is rare and the mortality rate extremely low. Reduction by enema is valuable in early cases. The tumor should always be palpated; under pressure from the enema it disappears; the loops of intestine immediately above become distended with fluid; the distention is general and symmetrical; and the return flow contains gas and feces. A somewhat similar procedure[73] consists in the reduction of the intussusception by air pressure. The air is introduced through the anus after the abdomen is opened and the mass is in the hands of the surgeon for proper control. The intussusception unrolls well until the point or origin is reached where edema may make manual assistance necessary. Measures to prevent recurrence such as fixation of the cecum or ileum are unnecessary. It is to be particularly remembered that the enema treatment is dangerous in late cases where portions of the bowel wall may have been so devitalized as to rupture easily. In irreducible cases, the mortality from resection is so much higher than when intralumenar slough and evacuation are permitted to take place that Fraser[4] is prompted to remind us that "Nature's surgery surpasses the handiwork of man."

In the treatment of intestinal obstruction, attention is being directed more to restoration of normal conditions by assisting physiologic functions than by surgery. Studies show that in high obstructions death is due to failure of secretions from the upper intestinal tract to reach the lower[74] and to the loss of important blood electrolytes.[75] There may be either alkalosis or acidosis, and nutrition is seriously impaired. Surgery is often useless or contraindicated, and the condition may be relieved by intravenous use of saline, Ringer's solution, Hartmann's solution, or glucose at appropriate times as indicated by blood chemistry tests.[76] Obstruction lower in the small bowel causes marked loss of fluid by increased secretion into the bowel, diminished absorption with demineralization, disturbed acid base balance, and neuromuscular upset. High enterostomy is not as effective as duodenal tube drainage. After low enterostomy is performed or a duodenal tube is in place, the bowel should be allowed to regain its normal function with a minimum of further interference from the physician or nurse. Treatment directed toward restoration of peristalsis should be withheld until drainage is established, and in this connection it should be kept in mind that intravenous hypertonic saline stimulates peristalsis and glucose retards it. When obstruction is due to strangulation, surgery is obligatory and early diagnosis is essential to a favorable outcome. Resection is to be used only if absolutely necessary, and exteriorization is of doubtful practical value. In the treatment of paralytic ileus, ileostomy is usually a futile gesture, and drugs and hypertonic saline have little value as peristaltic stimulants. Spinal or splanchnic anesthesia to paralyze the brake action of the visceral sympathetics at times produces spectacular results, but it is of little value in late toxic cases.

Continuous drainage by duodenal tube[77] is often a life-saving measure in simple obstruction of the small intestine, particularly of the adhesive type. It is also excellent for improving the general condition preliminary to operation. The insertion of the tube may take some time; its position can be controlled by x-ray observations. There should be many holes in the distal portion of the tube so that the stomach as well as the duodenum will be drained. Hot packs should be applied to the abdomen; fluid and nourishment should be supplied by intravenous injection of from 3,000 to 4,000 c.c. of saline and glucose daily; and peristalsis should be aided by salivary stimulation by ice, lemon juice, or chewing gum. In the relief of this frequently fatal condition, the development of continuous duodenal drainage is the most outstanding recent advance.

Continuous intravenous administration of fluid may be necessary in any condition where there is marked disturbance of fluid metabolism,[78] an excellent solution for general use being 5 per cent dextrose in Ringer's solution.[79] It protects the liver and kidneys, stimulates renal activity, relieves dehydration, and supplies valuable nonprotein constituents. It is advisable to use insulin, from 8 to 10 units to each 25 grams of dextrose, to avoid the inhibiting effect on peristalsis. The choice of method whether by cannula or needle and the choice of the vein to be used will depend upon the individual preference and experience of the physician. A vein may become reddened for an inch or two above the point of introduction of the fluid after a few days. Such reaction is usually chemical rather than bacterial, but it is an indication for change to another vein. If glucose is being used alone,

it should not be used continuously because it causes thrombosis.[80] The attempt to maintain a solution at such a temperature in the container that it will enter the blood stream at body temperature is not only doomed to failure but is unnecessary. The only precaution necessary is that the temperature of the entering solution should never be much above that of the blood, and for all practical purposes room temperature is satisfactory.

In the great mass of literature relating to appendicitis, a trend is becoming apparent to withdraw somewhat from the position that a patient should be subjected to surgery as soon as the diagnosis of appendicitis is made regardless of the stage of the pathologic process at the time. A thorough understanding of the pathogenesis of appendicitis[81] is necessary if the optimum time for surgical treatment is to be chosen. The fact that a condition happens to be surgical in nature is not necessarily an indication for operation and the tradition which has made the name "appendicitis" a major surgical indication is outworn. In the early stages when the pathologic process is progressing and the appendix is still the major focus of infection, its removal is indicated even if perforation has occurred and peritonitis is beginning. Later when peritonitis or abscess is the major pathologic process, the removal of an appendix which has done its damage and retired to a secondary position can do little if any good and in most instances will be actually harmful. The treatment of choice for an acute, violent, spreading peritonitis is not surgical trauma, and the mere fact that the process chanced to be initiated by a perforation in the appendix is not an adequate reason for reversing the treatment of choice. Much of the confusion regarding the treatment of appendicitis has been due to the failure to recognize the fact that the treatment of appendicitis is not the treatment of peritonitis which may be a result of appendicitis.[82] The mortality following appendectomy in the presence of general peritonitis varies from 18 per cent to 50 per cent while that following rational treatment of peritonitis is less than 10 per cent. Fowler's position tends to prevent distention, glucose in normal saline intravenously reduces peristalsis and supplies fluid and nutrition. Other essential parts of the treatment are heat to the abdomen, absolutely nothing by mouth or by rectum, sufficient sedation to give physical relaxation, empty the stomach by lavage, and use the duodenal tube for the relief of vomiting or upper abdominal distention. Paralytic ileus, secondary abscess, enterostomy, and fecal fistula are rare with this treatment.

It is difficult to accept loose statements regarding low resistance in children, for they recover from other infections easily.[83] The mortality rises in proportion to the time elapsed between the onset and operation in the acute cases. In the later stages when the process is localizing or has localized, delayed operation is preferable.

One explanation of the many faulty diagnoses of appendicitis is seen in the great number and variety of conditions, the symptoms of which have been said to resemble those of acute appendicitis. In one list no less than forty of these are enumerated.[84] It is evident that no clear conception of the actual picture of acute appendicitis based upon an understanding of the pathology could have existed in the minds of those who made these comparisons. The tendency to diagnose any condition which may be accompanied by discomfort in the lower abdomen as acute appendicitis is the probable explanation.

There are of course a number of conditions, the symptoms of which so closely resemble those of appendicitis that differential diagnosis is extremely difficult and in some cases impossible,[85] but this number is small as compared with forty.

A polyvalent serum made from several strains of the colon group and anaerobic bacteria isolated from bowel contents has been used in a small series of late appendicular peritonitis cases.[86] The mortality seems to be somewhat lower than the average for this condition, but the series is considered too small to be conclusive. The serum may be used intraperitoneally, intravenously, subcutaneously, or intramuscularly, and it is recommended that sensitization tests be made. If such a serum possesses antitoxic properties, it should prove valuable in cases which are in need of temporary assistance during the height of toxemia; but there should be no relaxation of the proved measures of treatment with a tendency to lean too heavily upon a possible neutralization of toxic products.

The effect of irritation and scar contraction upon the nerves of the appendix may be seen in reflex disturbances in many parts of the body.[87] The period of inflammatory reaction is followed by fibrosis in the submucosa,[88] which may be so extensive as to cause cicatricial obliteration of the lumen. The contraction of the fibrous tissue upon nerve endings or upon severed ends of nerves in an appendiceal stump can produce impulses comparable to those originating in the neuromata of an amputation. Such impulses transmitted through the visceral sympathetic system may well cause gastrointestinal symptoms such as pylorospasm, constipation, diarrhea, disturbance of gastric secretory balance with ulcer production, spasticity of abdominal muscles, and general nervous and neurotic symptoms. Such a condition may explain the great diversity of symptoms ascribed to chronic appendicitis and also the occasional persistence of symptoms after appendectomy.

Appendicitis in infants between twelve and eighteen months of age probably occurs with greater frequency than is commonly believed and presents unusual difficulties of diagnosis.[89] During the periods of paroxysmal pain, the infant appears very ill but seems fairly normal between them. Spontaneous pain is shown by pseudotenesmus when little or no stool is passed, and the presence of mucus is significant. Food will be taken eagerly for a short time and then refused with a sudden scream. In order to determine the presence of tenderness, the infant should be put to sleep with a sedative such as one of the barbiturates and the left side palpated first. The reaction to similar palpation on the right side is sharp and positive when the appendix is acutely inflamed. Coexisting pyelitis may complicate the picture. Distention is rare. An interval free from symptoms may indicate perforation. The occasional failure to localize tenderness to McBurney's point is due to the abnormal mobility of the cecum and the long appendix characteristic of the age.

A study of umbilical hernia[90] brings out the fact that in adults 16 per cent become strangulated, with a mortality of 33 per cent. In children the operative mortality is practically nil and only 11 per cent of umbilical hernias require operation. If the ring has not closed or shown satisfactory reduction in size by the age of eighteen months or if it still admits the tip of the little finger at two years of age, operative closure is indicated. Excision of the umbilicus is unneces-

sary. The tip of the little finger is a rather indefinite standard upon which to determine the necessity for surgery, and it would seem better to set a definite age as, for example, three or four years, after which nonsurgical measures cannot reasonably be expected to succeed. It may be stated definitely that the condition should not be permitted to exist beyond childhood.

The possibility of absorption of glucose by rectum in amounts sufficient to be of therapeutic value has been the subject of numerous studies over a period of years. Recent observations in diabetic and nondiabetic persons[91] appear to prove definitely that it is absorbed in appreciable quantities, and one case of insulin shock was treated successfully by this method of administration. The same conclusions have been reached in a series of carefully controlled observations upon colostomy patients.[92] In these patients conditions are ideal for such a study and the findings are remarkably exact and constant. On account of the location of the colostomy, the portion of the colon studied was the distal segment which is the less absorptive half, but in spite of this fact absorption varied from 9 to 20 grams in from three to five hours. Other substances absorbed were methylene blue, atropine, sucrose, and arsenic. In the therapeutic administration of glucose by rectum absorption may well be expected to be much greater on account of the fact that the solution can pass easily into the proximal colon, one of the principal functions of which is absorption.

Gallbladder disease, formerly thought to be rare in children, is being reported with increasing frequency.[93] Biliary colic occurs as in adults; there is tenderness over the gallbladder, rigidity of the right rectus, pain at the umbilicus or in the upper right quadrant, moderate leucocytosis, bile in the urine, and usually jaundice following repeated attacks. Chronic cholecystitis may develop[94] for which cholecystectomy is advised. In infants the occurrence of abdominal pain, fever, and leucocytosis is usually sufficient for a faulty diagnosis of appendicitis.[95] Stones may be formed before birth and be associated with a congenital stenosis of the common duct. The bile in some instances is thick, the supposition being that its increased consistency is due to muscular inactivity during intrauterine development.

Opinions regarding the time of election for the operative treatment of congenital diaphragmatic hernia vary. If the infant survives the first month of life, when 75 per cent of the patients die,[96] the condition may continue through adult life with few symptoms, strangulation being the chief danger.[97] Conservatism as regards surgery is counseled on the one hand and operation as soon as the general condition is good on the other. The operation is rather a formidable procedure but good results are reported in the favorable types. Diagnosis may be obscure for a time but roentgenography is usually conclusive. The route of approach may be thoracic, abdominal, or a combination of the two, depending upon the skill and preference of the surgeon.

CHEST AND LUNGS

In pulmonary abscess,[98] surgery is indicated if medical treatment fails. Pneumothorax is not advised because of the danger of rupturing the abscess into the pleural cavity. The medical treatment recommended consists of rest, posture, and medication for a period of two or three months, after which such surgical procedures as bronchoscopy,

pneumothorax, pneumolysis, or thoracoplasty may be tried. It would appear that there is little general agreement upon the treatment of this serious and disabling condition. Bronchoscopy should be used early to eliminate the possibility of a foreign body as an etiologic factor and to assist in removal of the contents of the cavity. Continuous postural drainage is often effective. The extremely disagreeable odor associated with most of these cases tends to minimize prolonged bedside study.

Nonopaque foreign bodies in air passages should always receive serious consideration in any case showing protracted pulmonary symptoms.[99] If seen early, the history is usually diagnostic. An asthmatic wheeze or other abnormal respiratory noises suggest foreign body in the larger air passages. Partial obstruction causes reduced motility and emphysema while complete obstruction causes edema and collapse of the lung. Vegetal bodies stimulate secretions markedly. In cases seen in the period immediately following the entrance of the foreign body, the old remedy of inversion and thumping upon the back should be studiously avoided as impaction of the foreign body between the vocal cords may occur with resultant suffocation before it can be extricated or a tracheotomy performed.

Congenital pneumothorax is a rare condition, the cause of which is unknown.[100] There is respiratory embarrassment at birth with cyanosis which may suggest a congenital heart lesion; the x-ray findings however are clear. The treatment which would seem logical—aspiration of the air—proved fatal in two cases. There was a sudden rush of air under pressure with collapse and death. Somewhat different in behavior is congenital air cyst of the lung.[101] There is intermittent cyanosis and dyspnea and the roentgenogram shows a cyst outline. Repeated aspirations, removing 4,000 c.c. of air upon one occasion relieved the condition slowly.

In the discussion regarding the relative merits of open and closed drainage in empyema, the custom has been too prevalent of reporting a series of cases all of which have been treated by one of the two methods.[102] The attempt has been made to force all cases to conform to one predetermined type of procedure regardless of individual differences, and, as a consequence, deductions and conclusions have been conflicting. The peaceful demise of this all too pointless discussion will probably occur as a logical result of the increasing trend toward better knowledge of physiologic reactions, requirements of body chemistry, pathogenesis of the disease, and the correlation of these factors in the study of the individual patient. Then will come the employment of open or closed drainage as individual conditions indicate.

The realization of the fact that the normal chest is a single cavity and that the mediastinum is freely movable has brought about a much more rational surgical therapy.[103, 104] The proportion of air going into a chest either through the trachea or through an external opening depends upon the relation of the size of the trachea to that of the opening. In the presence of an open thorax, important changes take place during respiration. There is a comparative increase in the size of the affected pleural cavity; there is a decrease in the amount of air entering the lungs producing a relative suffocation or anoxemia; and there is shock from the motion of the mediastinum. To effect healing, the lung must expand and fill the pleural cavity after evacuation of the pus. This expansion takes place by the formation of

adhesions which creep slowly along the thoracic walls dragging the lung with them as they progress, and not by the control of intrapulmonic or intrapleural pressure. Empyema is not an emergency and the operation of choice should be done when the pneumonia has subsided, when pleural adhesions have formed, and when the mediastinum has become stabilized.

The mortality rate is lower in the summer and in the warmer sections of the country. It is highest in the age group under two years regardless of the method of treatment. It is interesting to note that the mortality follows the same age curve as in other surgical infections in children, for example appendicitis. In general the closed method is better for infants. They have a lower vital capacity and should have close pediatric supervision in the postoperative as well as the preoperative period. Pneumothorax should be avoided.

As regards the infecting organism; pneumococcus empyema is an end-product and occurs secondary to the original pulmonary infection; streptococcus empyema, an accompanying condition associated with other serious metastatic lesions, does not tend to localize, and the mediastinum remains unstable; staphylococcus empyema accompanies other staphylococcic abscesses and is serious.

The prognosis is based upon the following factors: (1) age, (2) type of infecting organism, (3) virulence of the epidemic, (4) complications or associated lesions, and (5) the general condition of the patient.

GENITOURINARY CONDITIONS

Malignant tumors in children occur with greater frequency in the kidney than in any other organ, 80 per cent occurring in the first two years. The diagnosis of adenosarcoma or Wilms's tumor[105] is usually not made until the abdomen becomes enlarged, as pain is rare and urinary symptoms are usually absent. Pyelography is essential both for diagnosis and for information regarding the opposite kidney. By the time the enlarged abdomen suggests the diagnosis, metastases have usually occurred and the prognosis is poor. Recurrence within a year following nephrectomy is the rule. Irradiation is of doubtful value as the radiosensitivity of these tumors is so variable.

Embryonal adenocarcinoma[106] is also practically symptomless. If nephrectomy can be performed before the capsule has been penetrated, the prognosis is fair. Neuroblastoma, a tumor of the sympathetic nerve tissue of the suprarenal medulla is nearly 100 per cent fatal within a few months. It occurs in infants and young children and is usually first apparent through metastases.

The expression "intravenous urography" should be supplanted by "excretory urography"[107] because of the development of substances for oral as well as intravenous administration. This diagnostic measure is of great value in lesions of the upper urinary tract and gives a fairly accurate estimation of function. It is especially applicable to work with children. Anomalies of the kidney and ureter frequently cause obstinate pyuria,[108] and a thorough urologic examination should be made if careful medical treatment does not produce results within a month. Pyonephrosis occurring in one portion of a kidney with double pelvis and ureter can give a confused picture, including gastro-

intestinal and urinary dysfunction with fever and referred pains; the diagnosis will often depend upon the excretory urogram.

Spina bifida occulta, causing enuresis or retention, is at times an important fact in urinary dysfunction.[109] Pressure or traction on the nerves, due to fatty deposits, fascia, or fibrous tissue, may be of sufficient extent to require surgical relief. If the symptom is enuresis, operation may be postponed until after puberty, but retention is more serious on account of possible dilation of the urinary tract. All other causes should be carefully eliminated before advising operation, and complete relief is obtained in only about 50 per cent of the cases.

Persistent incontinence which is not a true enuresis may be caused by urethral diverticula.[110] Cystoscopy and cystography are necessary for diagnosis and surgical removal, or the use of sounds gives satisfactory results.

Before renal surgery of any type is undertaken, a complete study of both sides is essential.[111] Some form of renal aplasia or hypoplasia is present on the side opposite the offending kidney in an appreciable number of cases, and under such conditions the treatment is necessarily conservative. The solitary kidney is particularly susceptible to disease.

A welcome addition to the resources at our command for the treatment of hypospadias is due to the renewal of interest in Ombrédanne's pouch operation.[112] Multiple stages are required, as is true of all forms of surgical correction of this deformity. The operations are perhaps easier for the general surgeon to perform than the steps devised by Blair[113] there is less probability of lateral leakage with formation of accessory openings, but there is slightly more risk of hair in the urethra and the appearance is at times so grotesque as to require cosmetic plastic surgery. The primary object of the correction is, however, normal function, and this is attained in an unusually high percentage of cases. Blair's procedures make use of the available tissues in a manner which is physiologically more correct, and in the hands of this master plastic surgeon give results which seem as near physical and physiologic perfection as is possible.

The treatment of choice for hydrocele is generally admitted to be excision, but when this is contraindicated or seems inadvisable, satisfactory results often follow the use of the injection of sclerosing solutions.[114] This treatment is contraindicated in the presence of inflammatory reaction and has the disadvantage of placing a destructive agent in uncontrollable proximity to important structures. Good results are reported following the use of 5 per cent sodium morrhuate to which 0.5 per cent phenol is added for preservation, such an agent being definitely preferable to pure carbolic acid, which has been used at times in the past. One injection is usually sufficient although repetition may be necessary.

The occurrence of undescended testis at birth has been variously estimated at from 10 to 30 per cent.[115] The majority of these descend during the first few weeks of life and additional ones up to the age of one year. After this however the chances of spontaneous descent are remote. Spermatogenesis may begin as early as the ninth year but is rarely complete before the fourteenth, and operation may be

performed at any convenient time before puberty, preferably from the ninth to the eleventh year on account of the small size and delicacy of the early childhood testis.

When the testicles cannot be found, the possibility of congenital absence is to be borne in mind.[116] This condition cannot be differentiated from complete cryptorchidism, until after puberty, and no attempt should be made to do so during childhood. Secondary sex characteristics develop in the cryptorchid but not in the anorchid.

Enthusiasm for the Torek operation for undescended testis is steadily increasing.[117] The excellence and permanency of the end-results are so uniformly satisfactory that other methods of treatment are to be considered only in the mildest cases. Failures are due to technical errors. Torek considers it necessary to attach the testis directly to the fascia lata in order to take advantage of the blood supply which develops from that structure. This is especially necessary if there is atrophy or tension. In extreme cases the testis may be brought down in successive stages,[118] three months or more being allowed for lengthening of the cord to take place between stages. When the condition is bilateral, both sides may be treated at one operation if time is a factor or such a course is otherwise desirable.[119] The technical difficulties of this procedure, however, are considerably greater than when one testis is brought down at a time.

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American Academy of Pediatrics

Proceedings

FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

June 11, 1934

Round Table Conference on Acidosis and Alkalosis

Leader: Dr. Alexis F. Hartmann, St. Louis, Mo. Assistant: Dr. Bengt L. K. Hamilton, Chicago, Ill.

The meeting was called to order at 9:30 A.M. at the Wade Park Manor Hotel by the chairman, Dr. Alexis F. Hartmann, St. Louis, Mo.

CHAIRMAN HARTMANN.—Acidosis may be defined as a condition in which there is either an undue accumulation of acid in the blood and body fluids or a loss of alkali; the opposite term, alkalosis, may be defined as a condition resulting either from an undue accumulation of alkali or a loss of acid. Distilled water ionizes into hydroxyl and hydrogen ions and is spoken of as having a pH of 7; that is the neutrality point where hydrogen ions and hydroxyl ions are equal in concentration. In a city like St. Louis, the water supply is treated by adding lime and ferrous sulphate, and it becomes very slightly alkaline in reaction so that the hydroxyl ions predominate over the hydrogen ions, the pH being about 8. The figure pH varies inversely with hydrogen ion concentration; as the pH figures rise from zero up to 14, the hydrogen ion concentration is falling. Just one numeral means a tenfold change in hydrogen ion concentration, distilled water containing ten times as many hydrogen ions as the tap water we drink in St. Louis.

The body fluids, such as blood and intracellular water, have a pH which tends to average around 7.4, somewhat in between the neutral distilled water and the slightly alkaline tap water. Should the body fluids suffer a change so that its pH becomes that of distilled water, death would soon occur. The patient could survive for a number of hours, perhaps a half day or so. On the other hand, should the hydrogen ion concentration decrease and the pH become anywhere near 8, there would be a severe alkalosis, incompatible with life. The terms, acidosis and alkalosis, really imply a shift in the blood from a normal pH of 7.4 toward 7 in acidosis and upward toward 8 in alkalosis.

What tends to prevent such changes from occurring in the body? That is an extremely important question in view of the fact that there may be variation in the intake of acid or alkali foods or in the formation of acid substances in the body. There are a number of defense mechanisms. The first one concerns the chemical composition of the blood and body fluids. These fluids contain certain chemical substances which are spoken of as buffers. Buffer substance is capable of absorbing a certain amount of acid without actually becoming more acid in reaction.

For example, if a small amount of hydrochloric acid, the strongest acid we know of chemically, is added to sodium bicarbonate, a reaction occurs with the formation of carbonic acid, H_2CO_3, in proportion to the amount of hydrochloric acid added. But this carbonic acid, being such a weak acid, does not dissociate into hydrogen ions readily. In other words, as far as pH change is concerned, the sodium bicarbonate has taken up this very strong hydrochloric acid and converted it into carbonic acid without allowing a very great shift in pH to result.

Protein is another important buffer substance in the blood and body fluids. Two types of protein exist in the blood, the plasma protein a combination of albumin and fibrinogen capable of taking up either acid or alkali without permitting a great change in pH. Their buffer effect against both acid and alkali is due to the fact that these proteins have carboxyl groups, capable of combining with the base of an alkali, and amino groups, capable of taking on acid. The other protein buffer is the hemoglobin in the red cell. Hemoglobin can and does bind base to act as a buffer substance against acid if it also gives up its oxygen. The proteins in the cells also act as buffers; in addition there are phosphates, both in the cells and in the plasma, which act as buffers. The phosphate which acts as a buffer against acid is the diabasic monohydrogen phosphate, Na_2HPO_4, which can be converted into the monobasic dihydrogen phosphate, NaH_2PO_4, without suffering a very great change in pH.

In summary, the body contains certain chemical substances which protect against acid and alkali accumulation and which are present in limited amounts in the cells, intracellular water, and blood.

What would happen if these chemical buffer substances were used up and more acid continued to be formed? The second defense mechanism concerns the activity of the kidney and there are two ways in which this activity functions. The kidney can put out urine, which is not so restricted as the blood in its reaction. The pH of the urine, for instance, goes well below 7; in fact, we know that it may reach 5 or a little under, and it can rise to 7.8, perhaps even to 8, under certain circumstances. By means of this greater latitude in reaction, the kidney is able to put out some acid by making the urine very acid and alkali by making it very alkaline. In other words, the alkalosis is tending to occur because of administration of sodium bicarbonate. If the kidney puts out a liter of urine at pH 8, the maximum alkalinity, urine would contain about 15 grams of sodium bicarbonate per liter. If the urine became less alkaline and was put out at the same pH as the blood, 7.4, there would be only 3 grams of sodium bicarbonate per liter. If it is put out at 7, the reaction of neutral distilled water, there would be only 1.5 grams of sodium bicarbonate per liter; at 6, 0.15 of a gram; and at the maximum acidity, pH 5, only 0.015. There is a tenfold change in the amount of sodium bicarbonate put out in the urine for each change of one numeral, 5 to 6, 7 to 8, in pH. It should be clear then how renal activity would control excretion or retention of alkali substance.

In acidosis, the urine becomes quite strongly acid and contains no alkali. If the kidneys are badly diseased, this excretory function fails, and the urine tends to remain more or less neutral. When the urinary pH is around 5, not only is sodium bicarbonate saved for the blood by not being excreted as such, but base which is in combination with other acids tends also to be conserved. Thus phosphate excreted in the urine will be monobasic rather than dibasic, and certain organic acids may be excreted practically unneutralized.

Another function of the kidney is perhaps even more important. When acid continues to pour abnormally into the body from one cause or another, and the alkali reserve, the bicarbonate buffer substance of the blood, has been reduced and

there has been gradual loss of base from the body because the mechanism for controlling the urinary reaction is not 100 per cent perfect, the kidney can stop further loss of such basic substances, which include sodium, potassium, calcium, and magnesium, by making alkali out of a neutral substance. The waste product, urea, going to the kidney can be converted into ammonia, and ammonia can be substituted for fixed base which is bound to the various acids due for excretion as they come to the kidney.

Let me explain that. Suppose we produce acidosis in a dog deliberately by injecting dilute hydrochloric acid intravenously. The sodium bicarbonate of the blood and body fluids would be reduced by the reaction with the hydrochloric acid. The urine would automatically become extremely acid so that no bicarbonate would be present in that urine. Chloride, however, would be excreted in the urine in the form of ammonium chloride and not as sodium, potassium, calcium, or magnesium chloride. Such increased ammonia excretion tends to occur also if acidosis is due to other types of acids.

There is still a third defense against a change in reaction of body fluid. The constant pH of the blood at 7.4 is due to the presence of two substances, the base bicarbonate and the free carbonic acid, this acid arising from oxidation in the cells and being simply CO_2 dissolved in water, giving H_2CO_3. When the ratio of base bicarbonate to carbonic acid is 20 to 1, which it normally is, the pH is 7.4. Suppose base bicarbonate were diminished from one cause or another, either from neutralization by acid or by actual loss from the body because of, let us say, loss of the alkaline pancreatic juice. The pH of 7.4 would be maintained if the body could reduce its concentration of carbonic acid in the same proportion as the base bicarbonate had been reduced, so that a ratio of 20 to 1 was maintained. Or, suppose we drank enough hydrochloric acid to neutralize three-quarters of the sodium bicarbonate of our body fluids. If we could get rid of three-quarters of the carbon dioxide, as fast as concentration occurred, we would still have a 20 to 1 ratio. That could be done by hyperventilation; if we breathe more so as to take in more outside air, which is very poor in carbonic acid and equilibrate our alveolar air with the blood as it goes through the lungs, we can reduce the tension of carbonic acid in our blood. That is the respiratory defense against acidosis. The respiratory defense against alkalosis would be just the opposite, diminished breathing permitting the carbonic acid to accumulate so as to maintain the base bicarbonate.

Of these three main types of defense, the buffer substance may be looked upon as the immediate chemical defense; the respiratory activity, as the fine adjustment defense; and the renal activity, as an aid to the conservation of buffer substance.

What are the acids ordinarily encountered and responsible for production of such changes; what are the associated clinical conditions; and what are the symptoms by which such conditions can be recognized clinically; how can we be sure of them by laboratory examination; and what can be done to prevent such changes or to relieve them?

The cases of acidosis and alkalosis in the St. Louis Children's Hospital in the period from 1923 to 1933 inclusive have been studied. In these cases the plasma CO_2 contents were determined in order to make the diagnosis. There were some 436 cases of acidosis and 107 cases of alkalosis; in all probability there was an equal number of cases that escaped such study. These cases can be divided into two groups: (a) *metabolic* types of acidosis and (b) *respiratory* types, and similarly in alkalosis, metabolic and respiratory types. We can dispense with the respiratory type of acidosis because the cases are rather rare; we did not observe a single case. We

probably would have if we had investigated newborn infants with asphyxia of one type or another or if we had investigated the few cases of morphine poisoning admitted to the hospital. On the other hand, there were two cases of respiratory alkalosis; in both instances there was marked primary hyperpnea.

The metabolic type of acidosis, the important subject, includes at least five different groups. The most important group is that associated with diarrhea and vomiting. In this group, the factors contributing to the acidosis are loss of alkali from alkaline intestinal secretions, marked anhydremia, which leads to circulatory and renal failure with the accumulation of certain acids, such as lactic and phosphoric. Of the 178 cases studied, the majority were associated with nonspecific diarrhea; this type, usually called cholera infantum, in which no specific organism can be recovered from the stools, is seen in hot weather in scrawny, malnourished babies, particularly when they have some infection outside of the intestinal tract.

There were thirty-four cases of acidosis associated with bacillary dysentery. Although the same factors are at play in the production of acidosis in bacillary dysentery, there is one more important factor. The intoxication seems to lead to ketosis through damage to the liver, which becomes enlarged and can be readily palpated. The accumulation of ketone acid becomes of some importance, therefore, in the acidosis associated with bacillary dysentery.

The next type was the group of seventy-nine cases of diabetes mellitus. The third important type was the nephritis group: nineteen cases in the acute stage of hemorrhagic nephritis, sixteen cases of severe "pyelitis," and forty cases associated with chronic renal changes that led to renal destruction and renal insufficiency. In the fourth type acidosis is associated frequently with very severe acute infections: for instance, seventeen pneumonia patients with a diminished alkali reserve were observed. Acidosis was also encountered in twenty-seven other patients with severe infections, particularly severe streptococcic infection of the nose and throat, leading to mastoiditis and septicemia.

Fifth, we have quite a number of other cases; seventy-one in all, that have to be subdivided into miscellaneous groups. The first subgroup, the cases of so-called nondiabetic ketosis, is rather interesting. These patients sometimes present the picture of cyclic vomiting or are admitted to the hospital in the fall of the year with a grippal infection, characterized by mildly red throat with bilious vomiting and marked ketosis. This perhaps represents the only group, other than the diabetic, in which the ketone acids are very important.

Nineteen children were found to have acidosis following convulsions. The cause there was anoxemia with lactic acid accumulation.

Then occasionally in heart disease we may find acidosis if there is a congenital heart lesion associated with marked persistent cyanosis which allows lactic acid to accumulate and if in the decompensation phase of rheumatic heart disease the circulation becomes so bad that anoxemia results. Four cases were the result of acid administered in an attempt at therapy, and ten were due to various other miscellaneous causes.

The metabolic type of cases with alkalosis is again the important type. There were forty-one cases secondary to vomiting due to obstructive causes. Of these, thirty-three were associated with congenital hypertrophic pyloric stenosis, and eight to intestinal obstruction or fistula. Next, severe nonobstructive vomiting cases accounted for twenty cases of alkalosis, and alkalosis resulting from alkali administration without an attempt to produce alkalosis occurred in twenty-two instances (a little later we will discuss how that came about), and in thirteen instances the

alkalosis was intentional, either as a therapeutic measure or for the purpose of study. There were some eleven cases due to various causes. Perhaps this analysis gives you some idea of the clinical significance of such cases.

CLINICAL CLASSIFICATION OF CASES OF ACIDOSIS AND ALKALOSIS
(St. Louis Children's Hospital, 1923-33, Inclusive)

ACIDOSIS (436 CASES)

I. Metabolic (Acid accumulation or alkali loss)
  A. Diarrhea and vomiting—178
    1. Nonspecific diarrhea—136
    2. Bacillary dysentery—34
    3. Intestinal obstruction and fistula—8
  B. Diabetes mellitus—78
  C. Nephritis—75
    1. Acute hemorrhagic (glomerular)—19
    2. Acute suppurative ("pyelitis") and acute toxic—16
    3. Chronic, with renal destruction—40
  D. Severe acute infection—34
    1. Pneumonia—17
    2. Sepsis—27
  E. Miscellaneous—71
    1. Nondiabetic ketosis—27
    2. Convulsions—19
    3. Congenital heart disease—6
    4. Rheumatic heart disease—5
    5. Acid administration—4
    6. Other causes—10

II. Respiratory (CO_2 excess)
  No proved cases

ALKALOSIS (107 CASES)

I. Metabolic (Alkali accumulation or acid loss)
  A. Obstructive vomiting—41
    1. Pyloric stenosis—33
    2. Intestinal obstruction and fistula—8
  B. Nonobstructive vomiting—20
  C. Alkali administration—35
    1. Accidental—22
    2. Intentional—13
  D. Miscellaneous—11

II. Respiratory (CO_2 deficit)—2

If we inspect some of these cases quite a number will be noted showing acidosis with various levels of electrolyte concentration and various concentrations of individual ions, depending in the first place upon the relative amounts of base and acid which had been lost, and in the second place on the adequacy of renal secretion and of circulation, and sometimes also on the amount of ketosis present. There was a great variety of clinical causes; in the last instance there was a peculiarly mixed picture, which will be discussed later, in which there were certain tendencies for the development of both acidosis and alkalosis with the resultant condition neither.

In order to discuss symptoms and treatment, we must go back to the outline of body defenses against change in pH with the development of either acidosis or alkalosis, namely, the buffer effect, renal activity, and then respiratory defense. The symptoms and the findings leading to the diagnosis of acidosis or alkalosis are dependent upon changes going on concerning these defenses. Also it is apparent that the treatment has to take into account these defenses and must be designed to maintain these defense reactions of the body.

OUTLINE OF TREATMENT OF ACIDOSIS AND ALKALOSIS

I. Measures to aid respiratory defense

A. Respiratory stimulants in the extreme type of acidosis with respiratory failure

B. Avoidance of respiratory stimulants other than CO_2—CO_2 inhalations (for alkalosis)

II. Measures to restore normal buffer values

A. In acidosis

1. Direct

a. $NaHCO_3$

b. Blood (for restoration of Hb and plasma protein)

2. Indirect

a. Na-lactate and other salts of organic acids { Na citrate; Na acetate—"alkaline" ash diet; $CaCO_3$; $SrCO_3$ }

b. Glucose or glucose and insulin when ketosis exists

c. O_2 when anoxemia exists due to pulmonary causes

d. Fluids when anoxemia exists due to dehydration and anhydremia

B. In alkalosis

1. Direct

a. HCl

b. $H_2CO_3(CO_2)$

2. Indirect

a. NH_4Cl

b. $CaCl_2$

c. NaCl

III. Measures to promote renal activity.

A. Diuretics

1. H_2O—saline and dextrose solutions—plasma protein—acacia

B. Material for chemical reactions

1. NaCl—{ NaCl, KCl, $CaCl_2$ }—Lactate-Ringer's solution

IV. Measures to relieve primary causes, such as diarrhea, vomiting, infections, etc.

Let us consider what the respiratory defense is and how the symptoms are connected with the respiratory defense. As the bicarbonate content of the body diminishes due to loss of alkali or to an accumulation of acid, the ratio of bicarbonate to carbonic acid tends to diminish and the pH tends to increase. The defense is hyperpnea. Its function is to wash out carbonic acid keeping the ratio of bicarbonate to carbonic acid normal, 20 to 1. Hyperpnea then becomes a symptom of acidosis. The breathing in acidosis is essentially deep breathing without a pause between inspiration and expiration and with very little acceleration in rate. The rate is scarcely ever more than 30 per minute, but it is essentially deep, pauseless breathing. Unfortunately, breathing as a diagnostic symptom of acidosis is not so very reliable, for a number of reasons. The respiratory center in babies,

particularly when they are very feeble, apparently fails readily, and what should be deep, pauseless, and somewhat rapid breathing, becomes less deep, less vigorous, and more halting, and, therefore confusing; that is, there may be respiratory failure at any time so that the typical hyperpnea of acidosis is absent. Such a failure is noted particularly in premature infants. There may be some primary reason for hyperpnea, such as severe toxemia, high body temperature, or sometimes just high external temperature; or a condition which stimulates the respiratory center, such as mildly increased intracranial pressure; or inflammation, particularly the early stage of meningitis, may be associated with deep breathing which looks somewhat like the breathing of acidosis. In primary hyperventilation, however, there tends to be occasional abrupt pauses between deep breaths, whereas, in the typical breathing of acidosis such pauses are absent.

The breathing in alkalosis tends to be just the reverse. In the metabolic type the bicarbonate is high, and the ratio of bicarbonate to carbonic acid tends to increase. The breathing is designed to allow carbon dioxide to accumulate to a higher tension in order to make that ratio normal, again 20 to 1. To allow for that accumulation of carbonic acid, the breathing becomes slow and shallow and is often very irregular, and looks very much like Cheyne-Stokes breathing. Babies with pyloric stenosis, who have very marked alkalosis, frequently show such breathing. The respiratory action cannot be noted unless they are examined closely, and then a few shallow breaths are observed and a long pause that may last from fifteen to twenty seconds.

When the breathing begins to fail in acidosis, respiratory stimulants may be of some value. They usually are ineffective, however, because the respiratory center having been whipped until it cannot work any more, is very hard to stimulate further. On the other hand, when there is a tendency toward hyperventilation in alkalosis, as there may be when the patient is disturbed by hunger or pain. The relative hyperpnea can be avoided with sedative drugs or the loss of carbonic acid through the lungs can be prevented by making the patient breathe in carbon dioxide at such a tension that he cannot lose carbon dioxide from the blood; really effective aid can be given the respiratory defense against alkalosis.

The chemical buffer values of the blood and body fluids act as a second defense: the bicarbonates and proteins, plasma proteins to some extent, but hemoglobin to a greater extent. A diminished alkali reserve can be restored in acidosis directly by giving the sodium bicarbonate, which has been lost or reduced. Protein buffers, particularly hemoglobin and plasma, can be restored by blood transfusions.

Alkali reserve can be restored indirectly, however, in a number of ways: we can give the sodium salt of an organic acid like lactic acid, or we can give sodium citrate, sodium acetate, calcium carbonate, or strontium carbonate, or simply a diet which contains alkaline ash. In some instances salts are preferable. In the acidosis of chronic nephritis in which phosphate retention is considerable, it is advisable to feed calcium carbonate because the calcium tends to prevent absorption of phosphate from the intestinal tract, and thereby reduce the phosphate retention in the blood. Strontium works similarly for sulphate. In cases of ketosis the alkali reserve can be restored indirectly by burning up the acetone bodies, by keeping them from forming by the administration of glucose or by the establishment of glucose oxidation with insulin.

When anoxemia exists in pulmonary cases which would influence the metabolism of acid, particularly lactic acid, oxygen should be administered; but when the anoxemia is due not to a pulmonary cause but simply anhydremia with poor blood circulation, fluid is needed more than oxygen. Sometimes the oxygen tent is used in such cases because of its cooling effect. If fluid administration increases the

blood volume for a while, it will improve the circulation so that anoxemia tends to disappear and subsequent oxidation of certain acids occurs so that indirectly the alkali reserve is restored.

In alkalosis the alkali reserve can be decreased directly by giving hydrochloric acid. If it can be absorbed, it may be given orally, otherwise, it should be given intravenously. Carbon dioxide can be administered directly to restore the normal ratio. On the other hand, a high bicarbonate value may be reduced indirectly by the feeding of ammonium chloride, the ammonia being converted into urea in the liver and the chloride acting like hydrochloric acid, or by calcium chloride, the calcium not being so well absorbed as the chloride, or by sodium chloride. Sodium chloride works chiefly as a result of renal activity. This brings us to the third method of treatment directed toward promoting renal activity.

Certain substances which promote renal activity: first, the diuretic substances, one of the best of which is water. When water cannot be taken by mouth, it can be administered in the form of saline solution or dextrose solution. There are some instances in which the administration of salt water would lead to edema, particularly if there is a low plasma protein level. That, of course, sometimes confuses matters so far as renal activity is concerned. Occasionally plasma protein has to be given in order to cause diuresis, or a substitute for plasma protein, acacia. When water is being given to provide for renal activity, chemical substances should be included for the kidney to work on; these would permit it to retain those substances needed for the body and to excrete others not required. The first substance ever used, isotonic sodium chloride, is at our disposal. Simple Ringer's solution, sodium, potassium, and calcium chloride, and certain modifications of Ringer's solution, such as physiological buffer salts solution, which perhaps can be spoken of more simply as lactate-Ringer's solution are also available. Until now we have been talking about acidosis and alkalosis as symptoms of body changes which are secondary to some sort of disease, such as diarrhea, vomiting, infection, diabetes, nephritis, etc. Also we have to be thinking about measures which might relieve the primary causes of these troubles; that brings us to the fourth problem. Some of the things we have to work with, and from which we must choose are these: On the left of the chart is pictured the electrolyte composition of normal body fluids. On the extreme left is shown what is known about muscle fluid. The base is largely potassium; there is considerable magnesium present, not so much calcium, and a relatively small amount of sodium. In this muscle fluid there is very little chloride so that the base is bound to some other acid, the identity of which is not well known. The base of intercellular fluid is largely sodium; there is also some potassium and some calcium and magnesium. The base is largely bound to chloride and to bicarbonate. The base of the red blood cell contains only potassium and magnesium, no sodium or calcium. The chloride concentration of the red blood cell is much less than the intercellular water, and the hemoglobin protein substance neutralizes a good part of the potassium.

We are more familiar with the blood plasma or the serum itself because that is a substance we usually analyze. The base is largely sodium, but there is also potassium, calcium and magnesium; about two-thirds of it being bound to the chloride ion; about one-sixth to the bicarbonate ion; about one-tenth to protein, and the rest to such acids as phosphoric, lactic and other organic acids.

When acidosis or the metabolic type of alkalosis occurs, a complex picture has been brought about which, in addition to the loss of water from the body, includes the loss of various bases in, of course, different degrees in different individuals. It also includes changes in the concentration of such important anions as chloride

and may be associated with retention of such anions as phosphate and sulphate or the appearance and retention of some new substances, such as the ketone acids.

It does not seem likely that the administration of normal saline solution of 0.9 per cent sodium chloride will right all those complex changes, even though one of the most important changes is the loss of water and sodium chloride. However, if sodium chloride solution is given, the substances chiefly affected, base chloride and water, can be restored and at least a start is made toward righting more complicated changes.

Going a little bit further and using Ringer's solution, one can see what more may be accomplished. The first Ringer's solution used was somewhat hypotonic, being isotonic for frogs. Potassium and calcium were added; bases that have been lost besides sodium and relatively more water were added because of the hypotonicity. Locke and Tyrode further modified the original Ringer's solution to form the Locke-Ringer and Tyrode-Ringer solutions by adding some bicarbonate to the solution and magnesium in the case of Tyrode's solution, together with dextrose. Whether such solutions are much better than ordinary Ringer's solution is doubtful, with the exception perhaps of Tyrode's solution because the amount of bicarbonate which can be added directly is not very large. It is impossible to add as much bicarbonate as normal intercellular fluid has as it will not stay in solution. The calcium bicarbonate precipitates out, and such a solution could not be boiled to sterilize it. The bicarbonate would be changed into the more caustic carbonate.

We have prepared a hypotonic Ringer's solution, which contains sodium, potassium, calcium, magnesium and chloride, to which we have added an amount of sodium lactate equivalent to the normal amount of sodium bicarbonate in the blood; we have called this lactate Ringer's solution, which is still somewhat hypotonic.

There is also a solution, artificial spinal fluid, which will not be discussed, and on the extreme right of the chart, we have isotonic sodium lactate, one-sixth molar sodium lactate solution. Sodium bicarbonate represented in the same way would be about 0.5 per cent; it could be called isotonic sodium bicarbonate.

How to use these things most effectively is interesting. Perhaps this can be shown best by demonstrating the progress made in our knowledge during the last ten or eleven years. In one of our earliest cases of severe diabetic acidosis, before we knew whether alkali was necessary when we were going to use insulin, and if so, how much alkali was indicated, the CO_2 on admission was about 15 volumes per cent, and the blood sugar was quite high, around 670 milligrams per hundred cubic centimeters. Thirty units of insulin, the old H units, were given and 10 grams of sodium bicarbonate injected intravenously as soon as it could be prepared, and then insulin was repeated at about four-hour intervals, the next two doses being 35 units each. Therefore, during the first eight hours the child received 100 units of insulin with 10 grams of sodium bicarbonate intravenously and one more gram each hour by mouth for 10 doses. The plasma bicarbonate curve, first showed a very nice rise from 15 volumes per cent on up to 50 in about the first ten hours. At the same time the blood sugar curve went down, and the blood sugar was practically normal after twelve hours; the acetone excretion of the urine about disappeared in fifteen hours; and the urinary sugar also about disappeared in that time. We were extremely fortunate in this case because we just hit upon what happened to have been about the right combination of alkali and insulin.

We did about as well with the next case—an older girl—but one new point was brought out. After the initial insulin administration at 7 P.M., the blood sugar started coming down very, very rapidly. When we projected that rapid fall downward, and the rise of bicarbonate upward, the two lines could be predicted to inter-

sect at around ten or eleven o'clock in the evening., i.e., a blood sugar should have been down to normal when the acidosis was still quite severe. When that situation was noted during this part of the recovery, glucose in addition to the insulin was given to buffer up the blood sugar for a while. The bicarbonate curve continued on up, accelerating somewhat, and reached normal in around from twelve to fifteen hours. But another thing of interest was that when the first urine was put out at one o'clock in the morning, there were no acetone body acids present, or very, very little. These were quantitative measurements, i.e., from seven o'clock to one o'clock the oxidation of acetone body acids was almost complete. Some blood studies on this particular case with quantitative acetone body acids verified that statement. Here is one instance then in which when the first urine was passed, ketosis seemed not to exist, but it really was present as the blood studies indicated, and the amounts present were significant. The main point of interest was the slowly rising CO_2 and the rapidly falling blood sugar, which seemed to need buffering.

For about five years patients with diabetic acidosis were treated according to the Joslin scheme and given no alkali. An example of the recovery of such patients is shown in another chart. The organic acids are indicated in the light area marked "B." One can see how much organic acid is present circulating in the plasma when the CO_2 content is as low as it is. If bicarbonate were added to the organic acid you would have a total amount about equal to the normal bicarbonate. In this particular instance the amount of organic acid circulating almost quantitatively accounted for the reduction of bicarbonate, but sometimes it is much less and sometimes it is more.

This patient recovered very slowly. Six hours elapsed and, although the blood sugar had dropped very much and dehydration had been overcome, all the symptoms of severe acidosis were still present. After twelve hours the CO_2 was up a little, but the patient still had hyperpnea with a rapid pulse; after eighteen hours the CO_2 was perhaps out of the danger zone. It was several days before the CO_2 content was anywhere near normal. This was due to the fact that in such an instance almost the entire recovery from the acidosis is based on the oxidation of ketone acids which requires time and which is a function of glucose oxidation and insulin administration. We do get some help a little later from renal activity as the result of the excretion of acid bound to ammonia in the urine, but renal activity also requires time.

Can we help such a situation by trying to promote renal activity with the salt solution administration? This patient perhaps is not a fair example because she did unusually badly. After treatment with insulin was started, 30 units followed almost immediately by 20 units, a little later by 50, 30, 15, and the like, the acidosis actually became worse and the organic acid stayed high. During that phase Ringer's solution was given to try to get the effect of kidney excretion of chloride bound to ammonia. I think this patient did so badly not, of course, on account of the salt, but because she was insulin resistant and needed very large doses of insulin to accomplish good acetone body acid oxidation with release of base. The main point in this instance, as in many others, is that the addition of sodium chloride to the glucose and insulin therapy did not help matters much. In other words, while renal activity is extremely desirable, it is sometimes slow and not so very effectual.

On the other hand, if we return to our original method of treating such cases, by giving them an initial dose of sodium bicarbonate along with insulin, dextrose, and saline solution, it is a matter of only one, two, or three hours before the CO_2 content is out of the danger zone, the hyperpnea disappearing, and the pulse rate

dropping to somewhere around normal again. There is danger in this; another patient who was given both a fairly large dose of insulin, so that the blood sugar came down to the hypoglycemic zone, received too much sodium bicarbonate, with a resulting CO_2 content of over 100 volumes per cent. The child had been too successfully treated for diabetic acidosis. The bicarbonate value which was low was made very high, so that alkalosis was precipitated, and the sugar which was very high was made too low, but of course the ketone bodies were oxidized. Is the danger so real that we should not use alkali, and can we prevent such later development of alkalosis and still make use of the good effects of the alkali? Those are essential questions.

Let me show you that we can, because this chart is an illustration of the type of recovery we are seeing at the present time. This is an extremely simple method of treatment of this type of acidosis. On admission, with the very low CO_2 content, the patient was given the following substances: 60 c.c. of one-sixth molar sodium lactate, approximately one-half being given intravenously and the rest being given subcutaneously and intraperitoneally. At the very beginning of the treatment insulin was supplied in this dosage: 1 unit per kilogram subcutaneously, and the other unit per kilogram being put in the lactate solution and given intravenously. It took from one-half to three-quarters of an hour to administer that amount of fluid—to about one o'clock. The CO_2 content at two, three, four, and five o'clock in the afternoon reached 50 almost in a straight line. The glucose came down relatively slowly because of the glycogenic effect of the lactate. This was a large child, almost adult size, and in another very small child, just two and one-third years of age, the same thing happened; CO_2 content began with 10 volumes per cent. The treatment was two units of insulin per kilogram at the beginning, one subcutaneously and the other intravenously. Same dosage of lactate, 60 c.c. of one-sixth molar per kilogram, followed as soon as possible by the administration of a chloride solution, which can be either normal saline solution, or Ringer's solution, or Ringer's solution with the small amount of lactate (lactate-Ringer's). This child was admitted at 9 A.M., and by 11:30 A.M. the CO_2 content was up over 40 volumes per cent, and the hyperpnea had disappeared; the blood glucose was coming down pretty well to normal, and the lactate injected showing evidence of rapid metabolism so that in about four hours the blood glucose had reached almost a normal value, lower than it was when the patient came in.

How does the lactate solution work and just why do we use it instead of bicarbonate, which seemed to have worked all right too? This is the principle: When lactate is injected, the lactate diffuses out into the body fluids and becomes metabolized. One-half is converted into liver glycogen; the rest of it is oxidized, and a very small amount is lost by excretion into the urine. The metabolism of the lactate, including glycogen formation in the liver and oxidation, sets free the alkali gradually over a period of several hours. If about one-half of the solution is given intravenously over a period of from thirty-five to forty minutes, and if the remainder is put in subcutaneously and intraperitoneally, almost four hours are required for complete metabolism. There is, therefore, a gradual formation of sodium bicarbonate which goes far toward removing one of the dangers of alkalosis. We introduce sodium bicarbonate as carbonic acid accumulates, and at the same time liver glycogen is restored and the equivalent of glucose solution given. The effect of the sodium lactate is really double; it is a slow alkali former and is potential glucose so that additional glucose is not needed. In fact, the amount of lactate given in such cases, 60 c.c. of molar solution per kilogram of body weight, accounts for just about half the insulin we gave initially.

There were eighteen cases of severe acidosis—so severe that the CO_2 contents were under 25 volumes per cent to begin with, many of them under 15 volumes per

cent—treated without alkali of any type, being given insulin, glucose, and saline solutions. The amount of insulin given varied from the highest which was around 5.5 units per kilogram during the first eight hours down to 0.8 of a unit per kilogram. The average was 2 units per kilogram in the first eight hours. The various speeds of recovery and rise in CO_2 content were plotted against time and hours. There is no relationship between the speed of recovery and the size of the dose of insulin given. For instance, Patient 18 recovered most rapidly of all with the smallest dose of insulin, and Patients 1 and 3, receiving the largest amounts of insulin, made very slow recoveries. Two others actually became worse for a while before they began to recover.

The speed of recovery in patients receiving sodium bicarbonate is distinctly faster; none got worse at first. They all began to show recovery immediately, and there was a better correlation between the speed of recovery and the size of the dose of sodium bicarbonate given. The dose of insulin given was comparatively the same, averaging a little more.

There was a still greater speed of recovery in the sixteen patients receiving lactate, and there was a much better correlation between the size of the dose of lactate given and the speed of recovery.

The averages of the three groups of cases show that the lower curve is the average of the eighteen cases treated without any alkali, meaning that for each hour that elapses after the beginning of treatment the CO_2 content is expected to go up about 1 volume per cent for about the first four hours; then there is some acceleration so that after eight hours of treatment, the CO_2 is up almost 11 volumes per cent. If treatment is started at eight o'clock in the morning, when the CO_2 content is 10 volumes per cent, at four o'clock in the afternoon the CO_2 should be about 20 or 21 volumes per cent, still in the zone of fairly severe acidosis, and continued hyperpnea and tachycardia.

On the other hand, the average of the eight patients receiving sodium bicarbonate showed very much more rapid recovery, and the average of the group receiving sodium lactate showed still more rapid recovery. When lactate is given, you can administer safely about twice the amount of this potential alkali as you can of sodium bicarbonate because it is formed more slowly. Perhaps we could have speeded up the recovery of the bicarbonate group with safety. But we know we can do it safely and rapidly with the lactate; that is, in one hour the CO_2 can be raised about 9 volumes per cent and in two hours about 15 volumes per cent, and more can be accomplished in two hours than without alkali in eight hours, and the slope of the recovery curve is about what is wanted, a fairly rapid rise, tapering off as the normal CO_2 content is being reached.

The final outcome of all the cases shows that actually the mortality in the three groups was pretty much the same. There were 79 cases including those of mild acidosis along with those of severe acidosis. There were four deaths out of forty-five cases in which no alkali was used; one death out of ten in which sodium bicarbonate was used; and two deaths out of twenty-four (and we have added four more cases this year without any deaths) in which lactate was used. It is interesting to go into the cause for those relatively few deaths. The death of the child with the mild acidosis was due to pneumonia. The other three deaths apparently occurred as the result of acidosis, which was not relieved by the time of death, and yet from fifteen to twenty-four hours had elapsed before death occurred.

The single death in the bicarbonate group was associated with severe infection, as was one of the two instances in the lactate group. The other death was attributable to the manner of treatment. That was before the necessity of giving lactate as an isotonic (one-sixth molar) solution was understood. In this instance it was

given as a molar solution when the patient was already dehydrated. The temperature rose from 38° C. to 45.5° C. while the CO_2 content was increasing from 7 volumes per cent to about 35. Death occurred apparently from hyperpyrexia.

The best of the three methods of treatment can be chosen. If the patients are strong enough to survive hyperpnea for twenty-four hours or so, they will get along all right without alkali, but the recovery can be speeded up either by bicarbonate or lactate.

We had an interesting case in an eight-month-old baby. She was admitted with symptoms which were not recognized as diabetic acidosis. Ketosis was recognized, but it was thought she had an acetone-body acidosis associated with infection in her ears, and with some bronchopneumonia. Her sister had a similar infection but was not as sick. After a CO_2 content of 12.5 volumes per cent was noted, the infant was given the routine treatment for acidosis, 60 c.c. of one-sixth molar sodium lactate per kilogram, followed by chloride solution. The CO_2 content, in response to the lactate without insulin, rose from 12.5 volumes per cent to 25 in four hours; the urine was found at that time to be full of sugar and showed a very marked ferric chloride reaction. The blood sugar was found to be over 600. Insulin was given in the usual dosage, 2 units per kilogram, and the blood sugar, of course, was brought down and the CO_2 continued up. The reason this case is interesting is because the insulin was not given at the start of treatment. It is obvious the acidosis was considerably relieved with lactate even without insulin administration during the first six hours. This child recovered from the infection.

Let us summarize the diabetic situation. There has been lack of glucose oxidation, with ketosis and an accumulation of acetone body acids. Sometimes the accumulation is sufficient to restore bicarbonate after oxidation of acids. Sometimes it is not so great, and after the ketosis has been abolished, the CO_2 may still be low. In such instances alkali has to be supplied from another source—by giving salt, allowing the kidney to excrete the chloride and retain the base, or by giving alkali as sodium bicarbonate or sodium lactate; or we can take the cases as a group, not trying to find out whether they have marked ketosis and supply them all immediately with alkali followed by salt solution and insulin sufficient to abolish ketosis and bring the blood sugar back to normal. By that particular combination of supplying base, and bringing the blood sugar down we quickly relieve severe acidosis. The effect of chloride is not so much to aid in the recovery from acidosis but to prevent the development of alkalosis because one of the real reasons for the development of alkalosis in that type of case is a low chloride concentration with the eventual establishment of a normal base level which has to be maintained by some other anion, usually the bicarbonate ion.

Perhaps we ought to stop for a chance to ask questions.

DR. A. J. HIMMELHOCH (DETROIT, MICH.).—It was said that alkalosis does not occur very readily in pyloric stenosis, and I did not quite understand the reason.

DR. BENGT L. K. HAMILTON.—A recently published article showed that only a certain number of cases with severe pyloric stenosis did have an appreciable amount of alkalosis. You would, perhaps, expect all of them to have a severe alkalosis with vomiting. This author does not attempt to explain why they do not all get it.

CHAIRMAN HARTMANN.—Our figures as to the incidence of alkalosis in cases of pyloric stenosis have not yet been published, but the alkalosis can be missed easily unless the CO_2 content is determined. Since we have been accustomed to look for symptoms of alkalosis, particularly the breathing, we have recognized

them more frequently, and it is surprising how many babies are admitted with a CO_2 content over 100 volumes per cent, even as high as 120 or even 130 volumes per cent, without any signs of tetany, simply showing this depressed breathing. We found about 50 per cent of the cases with pyloric stenosis (they had been vomiting up to a week or more) having various grades of alkalosis.

There is another interesting point. After dehydration becomes extreme in such babies, the CO_2 content decreases again because of a secondary accumulation of phosphate, sulphate, and lactate, and sometimes ketone acid, which tends to neutralize the alkali excess. This is seen in intestinal fistula and obstruction more than in pyloric stenosis because in those instances the starvation is more complete and the dehydration tends to be more severe.

DR. W. H. THOMPSON (MINNEAPOLIS, MINN.).—If sodium chloride instead of either sodium bicarbonate or sodium lactate were administered, would the curve fall anywhere near the sodium lactate curve?

CHAIRMAN HARTMANN.—Not by any means. In the first group which was treated without alkali, the patients had salt solution administered with insulin and dextrose. If sodium chloride is given the effect on increasing alkali reserve will be due entirely to renal function, and the amount of ammonium chloride excreted depends upon the amount of urine, which, of course, depends upon time; also you are not always sure of the renal response.

DR. JOSEPH A. JOHNSTON (DETROIT).—David Kidd reported a group recently from Peter's Clinic showing a very rapid rise with salt. He was not averse to using soda; in fact, he left the question more or less open, but he did show that the majority of their cases treated with salt alone plus glucose did have a rise and had it very rapidly.

CHAIRMAN HARTMANN.—Only relatively so. He was contrasting the rise after salt with those cases that did not have salt. The rise was not just a matter of a few hours as we obtained here, but of days even in the best responses.

DR. JOHNSTON.—Yours is a more impressive group.

CHAIRMAN HARTMANN.—I should really have told you an interesting story about the two-and-a-third-year-old child. Her mother was extremely neurotic. That child had been seen about three weeks previously when it seemed the parents did not want to learn the child had diabetes and came hoping perhaps that I would tell them the child did not have diabetes. Instead I spent an hour telling them how important it was to know the truth to keep a record and do everything correctly. As a good moral, I told them what happened to one of our patients who left the hospital in good shape, but for whom Christian Science was adopted. That child died about a week later of acidosis. Can you imagine my surprise when at about eight o'clock one morning I had a call from the father saying the child was extremely drowsy, was vomiting a lot, and breathing very hard? He said about three days before they had quit the diet and insulin and had adopted Christian Science. The child came in at nine, and from then to nine-forty-five we gave the treatment of insulin, lactate, and Ringer's solution. At exactly ten o'clock when a postgraduate group I was scheduled to talk to on the treatment of acidosis met, I was able to show that the child was extremely hyperpneic. At five minutes to twelve, at the end of the lecture, I showed her again when the CO_2 had risen from 10 volumes per cent to 40 and she was breathing normally.

DR. JOHNSTON.—Could a clinical correlation be determined between the results with and without soda and the presence or absence of vomiting?

CHAIRMAN HARTMANN.—If there has been much vomiting during the development of acidosis, a greater chloride depletion should be expected. The first effect of salt solution administration will be retention of sodium chloride in the body. There will be no excretion of that salt in the urine until the chloride level and the base level have been restored. The full effect will not be obtained until the chloride level has risen, and that does not happen until a considerable amount of salt solution has been given. To answer your question directly—the amount of alkali to be used is directly proportional to the amount of vomiting. It is not always true that more acid will be lost when there is more vomiting. The vomitus from these children is not always very acid and, therefore, alkalosis does not always develop from the vomiting.

In considering the diarrhea group, one of the essential factors to be borne in mind is that a lot of pancreatic juice is not reabsorbed from the intestinal canal because of diarrhea. If a dog loses all its pancreatic juice through a tube in the pancreatic duct which allows the pancreatic juice to drain, the sequence of events is pretty much the same as in a child with diarrhea. The animal is all right for three or four days, then begins to get weak and drowsy, and on about from the seventh, to the tenth day, dies, very dehydrated and with very severe acidosis. The reason for the development of such acidosis is that the animal has lost a lot of pancreatic juice containing a lot of alkali and has not replenished the alkali as rapidly as it has been lost.

In diarrhea we are dealing not only with unabsorbed alkaline pancreatic and intestinal juices, but also with unabsorbed gastric juice, some of which may also be lost by vomiting. The picture is all mixed up. Let me recall some instances in which intestinal secretions were lost. In a case of intestinal obstruction there was very marked alkalosis with low chloride. Another case of intestinal fistula with both gastric and intestinal secretions lost showed very much the same picture. In so-called bilious vomiting seen sometimes in epidemics associated with pharyngitis and ketosis, despite the vomiting of gastric juice alkalosis does not develop because such an infection tends to diminish the secretion of hydrochloric acid into the stomach. In diarrhea there are different pictures, two cases of which showed phosphate and chloride well above normal values, but with a bicarbonate value tending to be diminished; this is the result not only of loss of gastrointestinal secretions but also of renal and circulatory failure.

Normal saline solution or saline plus dextrose solution may relieve this type of acidosis, but sometimes it does not work. For example, in the first three cases diarrhea continued; salt solution continued to be administered; but the acidosis in two instances tended to become worse, and in the other instance it was better for a while and then became worse again. That is no reason why salt solution should be discontinued. Salt solution really does not cause the increased acidosis per se, but in some instances it fails to accomplish what is expected. When the diarrhea is severe and continues, you may not be able to give enough salt solution to cause enough excretion of ammonium chloride into the urine to overcome this type of acidosis.

Sometimes a great deal more can be administered by a continuous intravenous drip, using sodium chloride and dextrose day and night with better results. But the point is, can it be relied upon? We believe it can be done much more simply, effectively, and safely in another way. The kind of case we are talking about is one in which the watery diarrhea continues and lasts for days and in which lots of saline and dextrose were given. After four days of treatment, the blood showed a very low bicarbonate content and a very high chloride content. As soon as this

was discovered salt was discontinued, but dextrose solution plus divided doses of sodium bicarbonate was given until gradually the sodium bicarbonate rose to normal and the chloride decreased.

In the next case the child developed a more severe acidosis under such treatment while in the ward, but with the judicious use of alkali we were able to accomplish what we wanted.

DR. JOHNSTON.—Was the vomiting or the diarrhea the prominent part of the disease?

CHAIRMAN HARTMANN.—There apparently had not been much vomiting in these cases. On the second day there was vomiting twice, but not large amounts, the third day only once, and the fourth day none at all. The history led us to believe that the child had not vomited very much previous to admission.

DR. JOHNSTON.—How can you tell how much alkali to give, and do you have to know that?

CHAIRMAN HARTMANN.—You can calculate an exact dose of alkali if you consider that the body fluids in general are in equilibrium with the blood; you can figure then that about two-thirds of the body weight is made up of such water. If the plasma CO_2 content is known from the patient's weight, you can calculate how much bicarbonate should be added to bring the CO_2 content up to normal. That is found by the final equation by estimating that the normal CO_2 content times three-tenths of the body weight in kilograms would give the cubic centimeters of molar sodium bicarbonate or molar sodium lactate required to bring the CO_2 content to normal.

If you use sodium bicarbonate, you may be inviting trouble because you may relieve the acidosis too promptly, with resultant alkalosis of the CO_2 deficient type and tetany. It can be done more safely with sodium lactate because the alkali is formed relatively slowly—that is, over the course of three or four hours. The effects of the lactate in normal individuals was determined, and the expected increases in CO_2 contents contrasted to those observed. The CO_2 contents did not rise quite as high as expected and averaged almost 5 volumes per cent short. The chief reason for this is that the moment the alkali is in excess in the blood there begins to be excretion of alkali into the urine.

In cases with severe diarrheal acidosis, we missed the mark even more; we always underestimate the need for alkali when the acidosis is severe from a few volumes per cent up to quite a large amount, almost 25 volumes per cent in some instances, and average about 12 volumes per cent short. This is due to a number of factors. These babies are very dehydrated. In addition to the lactate and its alkali effect, water is given; this increases blood volume and body fluids so that they actually gain in weight, and some of the bicarbonate which is formed is dissipated by dilution. Another reason is that this type of acidosis is usually uncompensated. The pH drops quite low and some of the buffers, particularly the protein substance, have yielded base to combine with carbonic acid; as bicarbonate and pH are restored this base is returned to these buffer substances, and such a shift would be one of the factors dissipating a rise in bicarbonate.

If we underestimate the mark with diarrheal acidosis, we do better in nephritis, and we may either underestimate or overestimate the mark in diabetic acidosis, tending to overestimate it if we also give insulin. It is essential to remember that if you give 60 c.c. of one-sixth molar sodium lactate, which is isotonic, enough potential sodium bicarbonate is given to increase the CO_2 content from 25 to 35 volumes per

cent. That should be a sufficient increase in the most severe cases of acidosis to bring them out of the danger zone. In the event the acidosis was not so severe, some degree of alkalosis might result, which should, however, produce no harm. We have adopted as routine the administration of 60 c.c. of one-sixth molar for the other types of severe acidosis also.

We have contrasted results in a group of cases treated without alkali, cases in which Ringer's solution and dextrose was administered, and in which satisfactory relief of acidosis occurred, with the bicarbonate-treated cases, and with the lactate-treated cases. There were few cases of acidosis satisfactorily relieved when alkali was not used. Perhaps that is arbitrary because we adopted as satisfactory relief of acidosis, a rise of CO_2 from the initial value up to normal or into the zone of mild acidosis within the first twelve hours of treatment. With just salt solution and salt and dextrose solution administration, it is rare to find a CO_2 returning to normal or to the zone of mild acidosis from extreme acidosis in twelve hours. On the other hand, one can accomplish this quite satisfactorily with either sodium bicarbonate or lactate. Also there were quite a few cases treated without alkali in which relief of acidosis was quite unsatisfactory. There were cases in which the initial CO_2 contents were noted but the course of recovery was not followed, and no data as to the speed of recovery was obtained. That comparison would indicate the superiority of lactate treatment over nonalkali treatment; also it is a little bit safer than bicarbonate treatment.

In nephritis the acute stage of acidosis may develop when there are acute cerebral symptoms with anoxemia and marked convulsions. The acidosis is really due to lactic acid, and when the convulsions cease, the lactic acid disappears and practically quantitatively restores the bicarbonate to normal.*

We can have a most interesting picture in acute hemorrhagic nephritis when associated with very marked vomiting and with sepsis. As a result of marked vomiting for two weeks previous to hospital admission in such a case, the chloride concentration had gone down, and the total base concentration was also quite low. The bicarbonate was just about normal. At one time, on about the third day, inorganic phosphorus reached 24.5 mg. per hundred cubic centimeters, which is a tremendous increase. After fluid was supplied in the form of saline and dextrose solution, particularly when the patient began to recover from the septicemia, there was enough healthy kidney remaining to provide good renal activity, and these marked chemical changes disappeared in about a week's time; all of which indicates that in the acute stage of nephritis, when urine is really being excreted, kidney function is good when we consider the way it can help in the maintenance of acid base balance. As the kidney tissue begins to disappear in the chronically active nephritis, and the patient has repeated infections losing a little more kidney each time, the chloride and total base tends to diminish more; the acidosis tends to increase and to persist. The persistence is due largely to the accumulation of phosphoric and sulphuric acids, together with the loss of a certain amount of base, both from vomiting, which tends to occur at intervals, and from polyuria. Apparently the urine comes down the tubules so rapidly that resorption is incomplete, and salt and bicarbonate tend to be present constantly in the urine. In other words, this urine tends to be neutral or even slightly alkaline, despite the fact that acidosis is present. Another important mechanism is being lost, the ability of the kidney to make ammonia and to substitute that ammonia for fixed base. As a result of all those changes we have the final picture characteristic of acidosis of chronic nephritis.

In a case of polycystic kidneys observed over a number of years, it was found that one kidney had never functioned because the ureter on that side was just a solid cord and the other kidney had perhaps a twentieth of the amount of substance

it should have had, and it was also full of cysts and scars. Over a period of a number of years all sorts of complex chemical changes resulted, due to persistent polyuria, bouts of vomiting, and frequent infections. That illustrates how important the kidney is in maintaining the acid base balance.

When alkali is given as lactate or bicarbonate in such cases to restore a diminished bicarbonate, the result can almost be calculated beforehand as the acidosis is slow in development, due largely to an accumulation of acid. When alkali is given, the chief effect is simply to restore the diminished bicarbonate. The average observed increase was only 1.7 volume per cent off from the expected, but we usually do not try to calculate exactly how much to give but use that same 60 c.c. of molar per kilogram in very severe cases.

We anticipated some trouble in this case. Treatment started when the CO_2 was down around 15 volumes per cent and brought it up to almost 40, the urine remaining around neutral. Another dose of lactate was given to put this patient up into a zone of alkalosis; we thought proof could be obtained that alkali should not be used in a patient with badly damaged kidneys because there would be no means of excreting the alkali excess. The result was that the excess alkali diminished promptly, and the alkalosis was short lived. The urine did not become very alkaline, however. Some of the base may have been passed in the urine bound to other acids; however, some may have been passed in the stools. There must be another defensive mechanism that comes into play in such instances.

Alkalosis associated with loss of gastric juice responds well to salt or Ringer's solution. The total base level is restored; the base bicarbonate is put out in the urine; finally the chloride level is restored; and chloride comes out in the urine. Another illustration of the same type of response shows that initially there was a low chloride and high bicarbonate with a pH reaction of the urine of 5.9, which would be about neutral to bromeresol purple—that is, a marked alkalosis with acid urine. This is an illustration of how little the reaction of the urine can be relied upon. In chronic nephritis with acidosis the urine tends to be alkaline because the kidney cannot excrete strongly acid urine. Alkaline urine, were it to appear in this type of alkalosis, would mean further loss of already reduced electrolyte. As chloride is given and the chloride rises and the total base level has been exceeded, additional base comes out in the urine, not at first as chloride, but as bicarbonate; the pH rises over 70, the urine becoming alkaline. Later chloride also appears in the urine.

In acute hemorrhagic nephritis there is good kidney function so that the same changes are permitted to occur despite the acute renal involvement.

In a patient with acute urinary tract infection, an alkaline urine was desired. Sodium bicarbonate was given intravenously, and excretion was forced at a maximum rate by also giving salt solution. The upper curve shows the pH of the urine and the chloride concentration, and the lower one the changes in the blood.

Suppose by mistake some alkali in the form of lactate is given a patient with alkalosis? This has been done deliberately in animals. Alkalosis can be produced by tying off the duodenum just distal to the pancreatic duct. After six days it will be observed that the chloride level of the dog has gone down to less than one-half, and the bicarbonate has gone up. If lactate-Ringer's solution is given, in time the chloride level will gradually be reestablished and also the total base, with excretion of the excess bicarbonate.

In thirty-one cases of pyloric stenosis the alkalosis was treated with lactate-Ringer's solution. Chemical data were obtained in about half of these cases. Some of these had CO_2 contents as high as 120 volumes per cent. A schematic draw-

ing shows the difference in the way in which Ringer's solution and lactate-Ringer's solution would be expected to act, and apparently does act in such cases. The usual picture of the plasma after marked loss of gastric juice by vomiting is a low total base but a greater relative reduction in chloride than total base with a correspondingly high bicarbonate value. If as much salt solution was given as would be necessary to bring the total base concentration to normal, that could be accomplished after the first injection of about 85 c.c. of Ringer's solution per kilogram and after around 100 c.c. of lactate-Ringer's solution per kilogram. Then the Ringer's solution would simply appear in the body fluids as base chloride, as Ringer's solution, and nothing would happen beyond that, except that the total base level would be restored. There would be no diminution of alkalosis, but there would be a little increase in alkalosis in the case of the combined lactate-Ringer's solution. That is, the lactate would have been formed into bicarbonate and would remain as bicarbonate because the total base level was only just approached.

If a patient is given more Ringer's solution and lactate-Ringer's solution the normal base level is exceeded and that extra base appears in the urine almost quantitatively as bicarbonate. That is after a second injection—though it might be after the third or fourth injection. The speed at which the alkalosis disappears is just the same in the two. There is a little lag, however, with the lactate-Ringer's solution. After the third injection, the normal base level and chloride level have been restored. Further administration of salt solution will be followed by the complete relief of the alkalosis plus the appearance of salt in the urine. That is about the way the two solutions work. There really is no need to be afraid of lactate-Ringer's solution in cases of severe alkalosis. But there is no indication for its use, for in such instances Ringer's solution is the solution of choice.

A child who for the first week had fairly marked diarrhea with a tendency toward dehydration was treated to prevent dehydration and acidosis by the administration of lactate-Ringer's solution, together with a feeding formula which was low in calories, chiefly protein milk to which lactic acid and sodium lactate had also been added. After about seven or eight days there was a change in the stools, the diarrhea began to improve and the weight began to increase. Soon it was apparent that the patient no longer needed any more parenteral fluid; it was stopped, but the weight gain continued and soon the patient was distinctly edematous. A type of low plasma protein edema had occurred because of the prolonged period of partial starvation attended by low caloric intake, poor digestion and assimilation. When the diarrhea stopped, salt and water were retained as edema fluid. For a while the factor toward reduction of dehydration overcame the factor toward production of edema. Anything given in the edematous phase depending upon the renal activity for its effect would not work. If salt solution was given with the idea of relieving alkalosis in such a patient, it would not work. If alkali was given for acidosis, even though buffered by salt solution, with the idea of not permitting alkalosis to occur, alkalosis would nevertheless occur. It is very important for renal function to be maintained and not be disturbed by low plasma protein. Some blood, therefore, is needed in the form of a transfusion to increase the plasma protein.

Another case showing edema following prolonged diarrhea was controlled by giving acacia, blood being given a little later. This patient's chest and abdomen gave the impression of dehydration. The ribs were prominent because of the loss of subcutaneous tissue. The skin over the abdomen could be picked up and stayed in a fold, but the extremities were decidedly edematous and the eyes puffy. After

blood or acacia is given to such a patient (acacia was given in this particular instance) the edema begins to disappear. The patient continued to improve, and after about four months he was really fine.

A general discussion on any phase of the subject is in order.

DISCUSSION

DR. A. C. KIRBY (LITTLE ROCK, ARK.).—In diarrhea, with extreme dehydration, what can be used to make up for lost fluids? I tried blood transfusions and insulin and glucose. The infants take plenty of water.

CHAIRMAN HARTMANN.—That is point IV in our outline of treatment. So far we have discussed the treatment of symptoms only. Both acidosis and alkalosis are symptoms of very complex changes in water and electrolyte balance. Measures have been designed to relieve those changes rapidly and to prevent their recurrence, but something will have to be done about the original cause of the trouble. There are some sick babies that nothing seems to help, but all patients with severe dehydration do not die; many of them recover. The cause of the diarrhea is important. In dysentery cases, the patient has a good chance if he survives the first week, because dysentery tends to be a self-limiting disease. If the diarrhea is associated with parenteral infection, such as rhinitis and otitis with mastoiditis, sometimes the cause may be removed by the treatment of the infection. A period of starvation for a few days is usually indicated, with continuous administration of fluid by the intravenous drip method. When administered, the fluids consist of equal parts of 10 per cent dextrose and lactate-Ringer's solution so as to supply dextrose and electrolytes necessary to maintain a normal acid base balance. A feeding very low in fat and carbohydrate, such as protein milk made up with lactic acid, is given at first in very small amounts and gradually increased. That is a problem of feeding and of diarrhea and, of course, lies outside the scope of our subject.

DR. KIRBY.—Most of the cases we see have gone on indefinitely until they are in a semicomatose state. Some of them live six or seven weeks, and you can pick up the dry skin on their legs.

CHAIRMAN HARTMANN.—The body can apparently stand just so much in the way of severe dehydration and severe acidosis. The babies may recover temporarily from both the acidosis and the dehydration, but something happens to the cells, and they eventually die. At autopsy sometimes one may find reasons for the death. But your observation seems to be just one more reason why severe changes like these should be relieved as promptly as possible, if one can do that safely, and then measures should be adopted which should prevent their recurrence.

You say, "What does it matter whether this particular diabetic child who comes in at noon is well at seven or eight o'clock at night or in two or three days?" It is important because he may have an infection with which he is just able to cope. How much more of a load will severe acidosis throw on him? How much better will he be if you relieve that load?

DR. KIRBY.—What form of alkali can be given by mouth?

CHAIRMAN HARTMANN.—We do not give alkali by mouth except in the chronic nephritis cases in which we can depend upon absorption, and then we use three different things. We use sodium lactate by mouth for its effect on the sodium bicarbonate content; calcium carbonate for its effect on the blood phosphate; and if the blood sulphate is high, strontium carbonate is given for its effect on the sulphate. Ordinarily we use from 10 to 20 c.c. of a molar lactate

orally three or four times a day. That supplies enough excess of fixed base over fixed acid. We give calcium carbonate and strontium carbonate, from 1 to 2 grams every three or four hours. We also try to give an alkaline-ash diet.

DR. WILLIAM McDOWELL (NORFOLK, VA.).—Is the lactate solution given intravenously or intraperitoneally?

CHAIRMAN HARTMANN.—The lactate solution is given subcutaneously, intraperitoneally, or intravenously. It should be approximately isotonic for subcutaneous and intraperitoneal administration. It may be somewhat hypertonic when given intravenously, and one should avoid a hypertonic solution intravenously if the patient is dehydrated. The material can be prepared or it can be purchased in molar form, which is six times the concentration to be used.

DR. T. L. BIRNBERG (ST. PAUL, MINN.).—How do you explain the edema of the hands and legs and the absence of edema of the other parts when the plasma protein is low?

CHAIRMAN HARTMANN.—This is typical of infants with so-called nutritional edema. I do not know how to explain it.

DR. HIMMELHOCH.—Do infants with nutritional edema recover regularly? We used to consider it almost a certain sign of death.

CHAIRMAN HARTMANN.—No, and in fact, I think the results are exceptionally good, for this reason: by the time edema occurs in that type of baby the original cause for the trouble has already been removed. The diarrhea and vomiting, being the original cause of course, starve the patient and lead to dehydration because of the loss of intestinal secretions. But by the time edema develops the diarrhea is a good deal less. In cases of fairly acute nonspecific diarrhea, extending from several weeks to perhaps a month or so, the prognosis is fairly good by the time the edematous stage is reached. But in cases of prolonged diarrhea due to bacillary dysentery there may be marked ulceration of the intestinal tract, and for this reason the prognosis may not be so good.

If real dysentery lasts so long with so much starvation and plasma reduction, usually there is extreme loss of mucous membrane over large sections of the bowel. We had two children who recovered very promptly. One had a case of Shiga dysentery, but it was a recurrence and seemed to respond remarkably well to bacteriophage.

DR. BIRNBERG.—I infer that you believe in long starvation periods?

CHAIRMAN HARTMANN.—If by long starvation you mean from twelve to perhaps seventy-two hours.

DR. BIRNBERG.—Isn't there a danger?

CHAIRMAN HARTMANN.—I think there is much less danger than giving food at a stage when they cannot handle it. They are more intoxicated and tend to become more dehydrated as the result of food administration. It simply adds to the amount of vomiting and diarrhea which further increases the loss of water and salt. Salt and large quantities of water with considerable dextrose can be given parenterally so that they can live for quite some time without regular feedings.

DR. HAMILTON.—Dr. Monrod, in Copenhagen, advocates starvation treatment up to ten days.

CHAIRMAN HARTMANN.—Is that routine?

DR. HAMILTON.—He starves them until all symptoms of intoxication are gone, and he considers albumin in the urine as one. That may be ten days; he has very good results.

DR. KIRBY.—That is a method of treatment throughout the country districts by practically all the country doctors.

DR. BIRNBERG.—In some types, long starvation increases the danger.

CHAIRMAN HARTMANN.—There is no doubt that both types are seen. In spite of starvation some continue to get worse and eventually die, and others show marked improvement and get along beautifully.

DR. C. CLARKSON PAYNE (DAYTON, OHIO).—Just what would be your treatment for a child who had been ill approximately ten days, with dehydration and diarrhea, watery stools?

CHAIRMAN HARTMANN.—We would assume that diarrhea of that duration sufficient to produce dehydration, would be associated with acidosis. If we had an opportunity to check the plasma bicarbonate, we would do so. We would administer 60 c.c. of one-sixth molar sodium lactate per kilogram of body weight. If the child is very dehydrated and about to collapse, intravenous injections are given to hasten the increase in the blood volume and aid the circulation. From one-third to one-half is the usual amount given intravenously. The rest is given subcutaneously and intraperitoneally, and then the administration of the lactate-Ringer's solution, is continued because it has a much smaller amount of lactate. If the patient is starved at the time, equal parts of that solution with 10 per cent dextrose are given. If the tendency to dehydration is extreme, the fluid is administered by the continuous intravenous drip method.

DR. BIRNBERG.—Do you believe in starvation for the treatment of the severe gastrointestinal disturbances due to parenteral infections to take care of the dietary factors?

CHAIRMAN HARTMANN.—There are at least two types of parenteral diarrhea. There is the epidemic type, such as we saw in 1925, occurring in healthy as well as in athreptic babies which was due to an acute upper respiratory infection by the streptococcus and which tended to involve the ears and mastoids frequently. I think in that type starvation is not very important; at least it did not seem to help our patients. The removal of the infection, particularly antrotomy, seemed to help that group a lot. Since then we have not seen so many of those babies; apparently that has been the experience of others too.

We still see a good many babies who have developed otitis media and a low grade chronic mastoiditis from an organism of low virulence; whose gastric juice is of very much diminished acidity; and for instance, whose gastric juice is teeming with colon bacilli. In such cases I believe that dietetic control, that is starvation, despite the parenteral infection, is very important and should precede the surgical treatment of the infection. When an antrotomy is performed on such a baby, I believe only about 5 or 10 per cent of the load is removed by the operation.

DR. R. W. HOLT (NIAGARA FALLS, N. Y.).—Do you ever use the intranasal catheter drip?

CHAIRMAN HARTMANN.—We have used it for a different type of dehydration than the one mentioned because vomiting would nullify the administration of fluids

intranasally. When diarrhea occurs, the absorption cannot be relied upon. But in other cases, such as burns, showing dehydration, that is a convenient way of administering fluid over a long period of time.

DR. BIRNBERG.—Where would you use the words "alkalosis" and "tetany"?

CHAIRMAN HARTMANN.—Tetany is a manifestation of alkalosis. But there are different types of tetany; the usual type is associated with rickets with low tissue calcium, but in alkalosis the diminished acidity of the blood and body fluids leads to a diminution of calcium ionization. There may be an ionic imbalance also at the same time, because of other factors. One can see how that would come about if the alkalosis was produced by sodium bicarbonate administration. As a result of those factors, the usual manifestations of tetany—an increase in neuromuscular irritability with muscular spasms or even convulsions—may appear. All cases of alkalosis are potentially cases of tetany, i.e., they may develop tetany if they have alkalosis. If babies with pyloric stenosis were left alone and could compensate with the diminished, depressed, irregular breathing, they could have very marked alkalosis without any signs of tetany, but should they have to hyperventilate from any cause so that the alkalosis would become less compensated, then signs of tetany are likely to appear.

The term "tetany" is used when there is evidence of increased neuromuscular irritability. Not more than about 10 or 12 per cent of those children showed tetany as an active symptom with the alkalosis.

DR. C. A. STEWART (MINNEAPOLIS, MINN.).—Since you have been using more lactic acid in severe diarrheal cases, what have been your results?

CHAIRMAN HARTMANN.—I think the results are improving because of the better method of handling the dehydration, the chemical changes, and the better method of feeding.

I haven't the figures with me, but as I recall there has been about a 15 per cent mortality rate in contrast with something like a 50 per cent mortality five or six years ago.

DR. STEWART.—Is it the diarrhea which does not improve?

CHAIRMAN HARTMANN.—Yes.

DR. STEWART.—Have you used periods of starvation for diarrhea?

CHAIRMAN HARTMANN.—Diarrhea seems to rid the stomach and upper intestine of organisms. It is still more effective to feed lactic acid buffered at a pH of about 4.6 with sodium lactate, about 1 per cent lactic acid, and ½ per cent sodium lactate, because colon bacilli do not grow well at that pH. It is enough total acid also to neutralize some of the alkali of the pancreatic juice, so that the duodenum should remain at about that same acidity. There are no direct observations to check that point.

DR. H. F. HELMHOLZ (ROCHESTER, MINN.).—Isn't that largely a matter of the stomach's failure to secrete a gastric juice to inhibit growth of bacteria rather than the growth of any organism producing the effect? There may be toxins produced, but it always seemed to me it was the other way around.

CHAIRMAN HARTMANN.—It is debatable whether the colon bacilli grow in the duodenum and stomach to cause a diminution of gastric hydrochloric acid or whether as a result of the disturbance, there is a diminution of hydrochloric acid which allows the colon bacilli to grow in the stomach and duodenum. Some work indicates that

certain strains of *B. coli* produce particularly toxic substances. The German literature records pathologic lesions appearing in the mucous membrane of the small intestinal tract, consisting of matlike deposits of bacteria in the mucous membrane which could cause rapid peristaltic movements. Also there is work to indicate that in the presence of an alkaline reaction in the duodenum, such organisms can be recovered from the thoracic duct, having made their way into the blood stream. At least that has been done in animals.

DR. HELMHOLZ.—That can be done in normal animals.

CHAIRMAN HARTMANN.—In one of your own early reports, you showed the frequency with which *B. coli* have been found in the urine of babies; that would indicate they got into the blood stream.

DR. HELMHOLZ.—Yes, unless they reached the kidney the other way.

CHAIRMAN HARTMANN.—It is also true the more you look for colon bacillus septicemia in those babies, the more you find it. It is a very common occurrence and sometimes leads to fatal colon bacillus meningitis.

DR. STEWART.—When a lactic acid preparation is given intravenously is any sudden change noted in the chemical composition of the urine?

CHAIRMAN HARTMANN.—In about one hour's time the urine has reached a good degree of alkalinity if the CO_2 was anywhere near normal to begin with. With the CO_2 down, the amount of lactate given may not have been enough to produce alkalinity in the urine. It depends upon the previous CO_2 content and the degree of dehydration. The first effect is almost immediate diuresis in a normal subject.

DR. McDOWELL.—What about acetone bodies?

CHAIRMAN HARTMANN.—We have not determined acetone bodies quantitatively. I think the lactate solution washes them out. I do not believe it actually increases their formation. There is a redistribution of lactate ions in the blood, body fluid, and perhaps cells, which seems to bring the other ions out where they can be excreted.

DR. JOHNSTON.—You can demonstrate that alkali actually inhibits oxidation in the normal. The effect is not just washing out.

CHAIRMAN HARTMANN.—Frequent statements can be found in the literature to the effect that alkali administration increases ketosis, and also that alkali administration causes the blood lactic acid to rise, but yet that has not been our observation. We have been unable to show any effect on lactate from alkali. We have not done enough quantitative blood studies to determine to our own satisfaction the effect of alkali on ketosis, but we have data from diabetes and from severe ketone acidosis where the main treatment was the administration of alkali in the form of lactate.

DR. JOHNSTON.—I think the argument does not apply at all to diabetes. In one case you are inducing an abnormal state of alkalosis and in the other you are approaching the normal pH.

CHAIRMAN HARTMANN.—Of course, you cannot have persistent alkalosis in a normal individual if there is no chloride deficiency. The normal cases we studied have all developed alkalosis from the dose of alkali given, but they did not maintain it very long, just a matter of a few hours.

DR. MC DOWELL.—Did I understand you to say that lactic acid was added to protein milk in some instances?

CHAIRMAN HARTMANN.—That is our routine first feeding in the diarrheal babies who do not have bacillary dysentery. The first food we give is made from dried protein milk diluted from 1 to 10, to which 1 per cent lactic acid and ½ per cent sodium lactate are added. The next step is to concentrate that milk and gradually add carbohydrate to it.

DR. O. L. STRINGFIELD (STAMFORD, CONN.).—What value has oxygen in the treatment of these cases of acidosis for liberating the CO_2.

CHAIRMAN HARTMANN.—That will be taken up in our discussion of therapy.

DR. PROCTOR C. WALDO (OAK PARK, ILL.).—Pneumonia is listed as giving rise to acidosis. Is it possible also to have alkalosis with pneumonia?

CHAIRMAN HARTMANN.—Yes, and I purposely did not want to confuse you by bringing up that point. Probably all the patients listed under "acidosis due to pneumonia" might properly have been placed in the CO_2 deficit type of alkalosis. The CO_2 content was in the zone of mild alkalosis, but we did not have enough pH values recorded on that particular group to be sure whether they had acidosis or alkalosis of the CO_2 deficit type, and your question is quite to the point. We might add also that we have yet to see a pneumonia patient in whom acidosis is really a clinical problem. It is not one of the important things to be recognized as far as chemical changes are concerned.

DR. MURRAY H. BASS (NEW YORK CITY).—We had a case of pyloric stenosis with profuse vomiting, depleted chloride, and a CO_2 content of 112. That child received sodium chloride subcutaneously and intravenously and recovered, but the values for the CO_2 came down much slower than the child improved clinically. Although the salt content of the plasma had increased quite rapidly, the CO_2 went down, as I remember, to 90 and then to 84, but much more slowly. Is there any particular reason for that?

CHAIRMAN HARTMANN.—That is the usual way it works.

DR. STRINGFIELD.—In the cases of severe alkalosis, especially where the CO_2 is around from 90 to over 100, is the breathing usually of a spastic shallow type and more relaxed than in severe acidosis?

CHAIRMAN HARTMANN.—The breathing may be jerky and irregular because of the tetany which may be present in alkalosis. Whenever a patient has alkalosis, there is danger of tetany. There can be increased neuromuscular irritability or actual convulsive movements which may cause jerky, irregular breathing or generalized convulsions, often with laryngeal spasm. That type of tetany is called alkalotic tetany and presumably is due to the increased hydroxyl concentration which tends to cause less calcium ionization. The calcium content of the blood is normal in such cases. If alkali were actually given to such patients in the form of sodium bicarbonate, in addition to the depletion of calcium ionization, there would be increased sodium ion concentration.

DR. HUGHES KENNEDY, JR. (BIRMINGHAM, ALA.).—What is the incidence of acidosis in cyclic vomiting? You say that cyclic vomiting may change over to alkalosis from acidosis?

CHAIRMAN HARTMANN.—The effect of vomiting as far as the production of alkalosis is concerned depends not only on the vomiting but on the amount of acid

lost. There are a number of conditions which seem to depress the secretion of hydrochloric acid in the stomach. Characteristic cases of cyclic vomiting do not show very acid gastric juice; and the patients may vomit a lot without losing much acid. Their vomitus is bile-tinged, so that they are losing in addition to the gastric juice, alkaline intestinal secretions. Then they have an accumulation of acetone body acids and perhaps are dehydrated also so that as a rule they do not have alkalosis but a mild acidosis.

If considerable chloride is lost by vomiting, even if it is in the form of salt as base chloride and not hydrochloric acid, when dextrose is given, the base that was bound to the ketone acid will be retained as bicarbonate regardless of the amount of bicarbonate formed from oxidation, as long as the chloride level is low, so that in recovering from ketosis such patients may sometimes show alkalosis.

DR. KENNEDY.—I had a child start out with typical cyclic vomiting and acidosis. Later the child developed alkalosis and carpopedal spasms with convulsions, which was attributed to the alkalosis and treated as such.

CHAIRMAN HARTMANN.—You mean an acidosis in which acetone was noted on the breath and ketone acid was found in the urine; but remember that the ketosis does not mean acidosis; this child may never have had acidosis at any time. Such a child usually develops acidosis, which depends not on ketoses but on the amount of acid and base lost by vomiting and the degree of acid accumulation. These are all such variable factors that it is difficult to predict in any one case just what is going to develop.

DR. R. A. DEVEREUX (West Chester, Pa.).—What effect does the continued administration of alkali have on the renal cells? Does the change of pH have some effect on the renal cells?

CHAIRMAN HARTMANN.—Continued acidosis may change renal cells, but there is no evidence of any change from administration of alkali. We know that in acute dehydration the cells are damaged.

DR. PHILLIP S. ASTROWE (Kansas City, Mo.).—You said something about giving ammonium chloride in the treatment of alkalosis by the indirect method. The ammonia radical is converted to urea, leaving chloride to act as hydrochloric acid. What is the mechanism of giving calcium chloride in the treatment of alkalosis?

CHAIRMAN HARTMANN.—When calcium chloride is given by mouth, the calcium is not as well absorbed as the chloride, staying in the bowel as calcium phosphate or some other insoluble calcium salt. There are two effects when it is given intravenously. The chloride is excreted by way of the kidney and the calcium by way of the bowel, acting similarly to hydrochloric acid administration. The other effect when it is given intravenously is for the calcium to be retained in the body tissue; that is why it is so very useful when these patients have tetany.

DR. DONALD C. MEBANE (Toledo, Ohio).—What is the effect of anesthesia?

CHAIRMAN HARTMANN.—Anesthesia has at least two effects. The early effect is hyperpnea producing a CO_2 deficit type of alkalosis, and later on the oxidation processes are interfered with, sometimes at least with accumulation of lactic and ketone acids.

DR. BASS.—Have you observed that a 5 per cent glucose solution causes diuresis when given intravenously? I saw a child who I thought had acidosis. Ketosis was

present with very deep breathing. The child received glucose before I saw her, and when she entered the hospital, I was surprised to find that the CO_2 was 54. She was still breathing very deeply.

CHAIRMAN HARTMANN.—Yes, that was probably a case of the toxemia I mentioned, with hyperpnea that is mistaken for compensatory breathing of acidosis.

DR. BASS.—After glucose in a saline solution was given she developed polyuria and continued vomiting. I believed, after the first twenty-four hours the child was losing more fluid than she received and was being dehydrated. I changed to your solution omitting the glucose, and the child recovered very promptly.

CHAIRMAN HARTMANN.—Did you use 5 per cent glucose in normal solution, that is, did you add glucose to normal saline?

DR. BASS.—I mixed 50 per cent glucose with 500 c.c. of saline solution.

CHAIRMAN HARTMANN.—If you added 50 per cent glucose to saline, you diluted the glucose ten times and produced 5 per cent glucose in saline solution, which is twice normal osmotic pressure. That is, you had an isotonic solution to begin with to which you added one very hypertonic. You were giving, therefore, a slightly hypertonic solution which would increase excretion of urine with dehydration.

DR. BASS.—I never saw that happen before. The child also had glucose in the urine.

CHAIRMAN HARTMANN.—That is another dehydrating factor. If glucose comes through in the urine, it carries water with it, because urine cannot hold a concentrate form of glucose more than about 5 or 10 per cent. So that for each gram of glucose excreted, from 10 to 20 grams of water will also be excreted. Equal parts of 10 per cent glucose and Ringer's or lactate-Ringer's solution make a mixture that is only slightly hypertonic, and when given to dehydrated babies does not cause glycosuria.

DR. ASTROWE.—Studies made at Johns Hopkins Hospital showed there is a tendency toward acidosis in newborns, and when difficulty arises in resuscitating these patients, the administration of CO_2 tends to increase the acidosis but makes them improve clinically.

CHAIRMAN HARTMANN.—That effect is more apparent than real. When one says there is a tendency toward acidosis in newborns, one means that the CO_2 content is lower than in an older infant or child, around 40 volumes per cent frequently. That is due to the very large cell volume, and you see it in the reverse. When the cell volume is low and plasma volume is high, the CO_2 is near the upper limit of normal; and when the plasma volume is relatively low and the cell volume is high, it is down. That is really not acidosis. There is a failure to ventilate properly, due to some type of respiratory abnormality. The CO_2 increases the hydrogen ion concentration enough to make them breathe better; no harm is done when a temporary carbon dioxide acidosis is produced, for there is a nice, fine adjustment defense in hyperventilation which gets rid of the excess carbon dioxide as soon as they stop breathing the CO_2 mixture.

DR. RUSSELL C. BOND (WHEELING, W. VA.).—In 1923 Dr. Hartmann was giving just glucose and insulin, and later when I was a medical interne and worked with the children he started giving bicarbonate, and in the eleven years the change has gone on. Two or three things have been brought out; I was taught to use sodium bicarbonate and how to figure out the actual dose of sodium bicarbonate and

insulin. We determined exactly how much insulin was needed to bring the blood sugar down to normal. I am greatly pleased today to learn the simple method of 2 units of insulin per kilogram and 60 c.c. of one-sixth molar sodium lactate.

A physician recently sent a year-old baby, who was quite sick, to the hospital. I diagnosed the trouble as severe acidosis. The history was that the baby had not been doing well. The baby choked on a tablespoonful of milk of magnesia that morning and had been breathing very rapidly since that time, gradually becoming unconscious.

At the hospital glucose in 250 c.c. of saline with 12 units of insulin was given under the skin. The urine showed the presence of sugar. The blood sugar was 484 milligrams per 100 c.c. We did not know the CO_2 value. I figured out a dose of 13 units since the child weighed 7½ kilograms. He was sitting up drinking orange juice by eight o'clock the next morning and has done very well. He has now had about 27 units of insulin.

CHAIRMAN HARTMANN.—He was one of the more favorable types. Some of them recover very rapidly.

DR. BOND.—I have enjoyed the privilege of working with Dr. Hartmann and watching the development of the present plan of giving sodium lactate in these cases, with 2 units of insulin per kilogram and transfusions.

I should like to ask about diabetic coma. Do you give insulin intravenously, or subcutaneously, or do you divide the dose?

CHAIRMAN HARTMANN.—We usually give half the dose intravenously and half subcutaneously, but the intravenous administration is prolonged over a period of some thirty minutes; it is probably absorbed just as rapidly, if not more rapidly, subcutaneously. When the insulin is administered intravenously, under ordinary circumstances you lose too much in the urine because of diuresis. There would be no substantial difference if it was all given subcutaneously.

DR. BOND.—Is the dose of sodium lactate determined just as we determine sodium bicarbonate from the CO_2?

CHAIRMAN HARTMANN.—Yes. That gives you cubic centimeters of molar solution. Ordinarily sodium bicarbonate is not calculated in terms of molar solution, but in terms of grams.

DR. BOND.—We have been using a 5 per cent sodium bicarbonate solution.

CHAIRMAN HARTMANN.—You can convert that into molar solution without much difficulty. The molecular weight of sodium bicarbonate is 84 so that a molar solution would be an 8.4 per cent solution, or 8.4 grams of sodium bicarbonate per 100 cubic centimeters. When you use a 5 per cent sodium bicarbonate solution, you use a fraction of a molar solution. The reason we do not calculate the lactate in terms of grams is because it is not a dry solid; it is hydroscopic and must be measured as a solution. It is better to designate the solution in terms of its molar strength because all other changes are really on that basis.

The session adjourned at six o'clock.

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES

(Conclusion)

Dispensaries

Thirty-three of the thirty-four children's hospitals included in this report maintain out-patient dispensaries. The dispensaries are associated with the hospital in thirty-one and in thirty are in the same plant. All except eight are in a residential district, in some instances a poor district, but in many a moderate or good district. Eight report that they are located in business districts where, of course, there is considerable traffic and noise.

Floor space and the number of examination rooms in the respective clinics vary considerably according to the average number of patients attending. One dispensary reports sixty examining rooms, another forty-seven; twelve have from ten to twenty; four have from twenty to thirty; ten report fewer than ten. All but one have at least one isolation room for suspected contagious cases.

Twenty-nine are open six days a week with the usual exception of Saturday afternoons, Sundays, and holidays. One is open five days and one, only four days. Two gave no reply. Prescriptions are dispensed at the dispensary in twenty-six instances.

The dispensaries are associated with the respective hospital in all but two instances. Table I reveals attendance figures for the various dispensaries and other facts of specific interest concerning them.

Summarizing the attendance figures one notes that the total attendance varied in respective dispensaries in the year 1932 from 852 to 84,202.

5 dispensaries under 15,000
6 dispensaries from 10,000 to 15,000
6 dispensaries from 15,000 to 20,000
3 dispensaries from 20,000 to 25,000
3 dispensaries from 25,000 to 30,000
2 dispensaries from 30,000 to 40,000
5 dispensaries over 40,000
3 dispensaries over 50,000
4 dispensaries over 60,000
1 dispensary over 70,000
2 dispensaries over 80,000

These figures, of course, reveal a considerable variation in the attendance in the respective dispensaries. Only ten have a yearly attendance of forty thousand or more and seventeen have an attendance of less than twenty thousand.

All dispensaries but two charge a fee at the first visit. The fee varies in price from ten cents to two dollars; the average fee is from twenty-five to fifty cents.

The attending staff serves in hospital and dispensary in twenty-six instances. In three of these only part of the staff serves in both hospital and dispensary.

All dispensaries keep complete case records.

All hospitals refer patients discharged from hospital to dispensary for follow-up.

Twenty-one dispensaries are used in teaching medical students.

Seven dispensaries accept patients who are able to pay private physicians. Twenty-six reject these.

TABLE I

DISPENSARY

HOSPITAL	DISPENSARY?	ASSOCIATED WITH HOSPITAL?	TOTAL ATTENDANCE LAST FISCAL YEAR	FEE CHARGED	DOES STAFF SERVE HOSPITAL AND DISPENSARY?	COMPLETE CASE RECORDS OBTAINED?	HOSPITAL DISCHARGED REFERRED TO DISPENSARY?	DISPENSARY USED FOR TEACHING?
1	Yes	Yes	78,955	.25	Yes	Yes	Yes	Yes
2	Yes	Yes	29,419	.50	Yes	Yes	Yes	No
3	—	—	—	No dispensary		—	—	—
4	Yes	Yes	38,269	.25 .10	Yes	Yes	Yes	Yes
5	Yes	Yes	13,047	Not fixed	Yes	Yes	Yes	Yes
6	Yes	Yes	68,330	.25	Yes	Yes	Yes	Yes
7	Yes	Yes	6,879	.50	Part	Yes	Yes	No
8	—	—	—	No dispensary		—	—	—
9	Yes	Yes	11,759	.60 *Co.	Yes	Yes	As indicated	Yes
10	Yes	Yes	852	.25	Yes	Yes	Yes	Limited
11	Yes	Yes	12,343	0	Yes	Yes	Yes	No
13	Yes	Yes	8,518	.50	No	Yes	Yes	Yes
14	Yes	Yes	67,466	.50	Yes	Yes	Yes	Yes
15	Yes	Yes	84,062	.25	Part	Yes	Yes	Yes
16	Yes	Yes	11,746	2.00	Yes	Yes	Yes	Yes
17	Yes	Yes	19,495	0	Yes	Yes	Yes	No
18	Yes	Yes	20,439	.60	Yes	Yes	Yes	Yes
19	Yes	Yes	28,349	.10 .25	Yes	Yes	Yes	Yes
20	Yes	Yes	19,995	1.00	Yes	Yes	Yes	Yes
21	Yes	Yes	3,000 plus	?	Yes	Yes	Yes	No
22	Yes	Yes	18,153	.50 .25	Yes	Yes	Yes	No
23	Yes	Yes	9,106	.25	Yes	Yes	Yes	No
24	No	—	Emergency treatment room maintained					—
25	Yes	Yes	21,139	.25	No	Yes	Yes	No
26	Yes	Yes	12,688	.50	Part	Yes	Yes	Yes
27	Yes	Yes	19,920	.25	No	Yes	Yes	Yes
28	Yes	Yes	37,220	.25	Yes	Yes	Yes	No
29	Yes	Yes	41,259	.35	Yes	Yes	Yes	Yes
30	Yes	Yes	19,558	.25	No	Yes	Yes	Yes
31	Yes	Yes	8,390	.50	Yes	Yes	Yes	No
32	Yes	Yes	24,049	.10	Yes	Yes	Yes	Yes
33	Yes	Yes	27,323	.25	Yes	Yes	Yes	Yes
34	Yes	Yes	84,202	.50	Yes	Yes	Yes	Yes
35	Yes	Yes	17,644	.10	Yes	Yes	Yes	Yes

*"Co."—County residents.

The replies to the question concerning the proportion of cases coming from over thirty miles away are interesting. Five reply that no patients come from over thirty miles away; including these five, nineteen report that 5 per cent (only 2 report 5 per cent) or less of their patients come from outside that radius. Surprisingly three hospitals report that 75, 50, and 80 per cent, respectively, of their patients come from over thirty miles away. Apparently these hospitals are state medical centers for the care of children.

Table II illustrates the dispensary organizations.

Summarizing this chart we note that all hospitals but two have out-patient dispensaries. Twenty have a medical director for the dispensary. The dispensary director is directly associated with the hospital in twenty instances.

TABLE II

HOSPITAL	MEDICAL DIRECTOR FOR DISTRICT	CONNECTED WITH HOSPITAL	PEDIATRICIANS	SURGEONS	OTOLARYNGOLOGIST	ORTHOPEDIST	OPHTHALMOLOGIST	DERMATOLOGIST	NEUROLOGIST	PSYCHOLOGIST	PSYCHIATRIST	DENTIST	ORAL HYGIENIST	ALLERGIST
1	Yes	Yes	23	7	12	9	2	3	3	3	0	10	0	2
2	Yes	Yes	10	3	5	3	2	2	1	1	0	7	1	2
3	—	—	—	—	—	No dispensary		—	—	—	—	—	—	—
4	Yes	Yes	21	2	4	6	2	1	1	2 combined		2	0	0
5	Yes	Yes	6	?	?	?	?	1	1	1	1	?	?	?
6	Yes	Yes	35	6	6	3	3	1	1	1	1	0	0	3
7	No	—	12	—	—	Not recorded		—	—	—	—	1	—	—
8	—	—	—	—	—	No dispensary		—	—	—	—	—	—	—
9	No	—	1	1	1	3	6	2	3	3	0	1	?	1
10	No	—	16 Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	No	Three orthopedic, general medical, and dental are only regular clinic persons.												
13	Yes	No	18	2	—	Use consultants			—	—	—	—	—	—
14	No	Yes	24	4	8	6	?	?	3	1	0	1	0	1
15	Yes	Yes	36	8	5	4	4	1	2	3	1	3	1	3
16	Yes	Yes	7	21	6	6	3	6	5	0	5	3	0	4
17	No	—	6	3	4	2	3	1	1	0	0	3	0	0
18	Yes	Yes	15	14	14	6	14	5	5	1	0	0	0	3

TABLE II—CONT'D

HOSPITAL	MEDICAL DIRECTOR FOR DISTRICT	CONNECTED WITH HOSPITAL	PEDIATRICIANS	SURGEONS	OTOLARYNGOLOGIST	ORTHOPEDIST	OPHTHALMOLOGIST	DERMATOLOGIST	NEUROLOGIST	PSYCHOLOGIST	PSYCHIATRIST	DENTIST	ORAL HYGIENIST	ALLERGIST
19	Yes	Yes	7	1	9	4	8	6	1	1	1	3	3	1
20	Yes	No	44	4	Part of large Gen. Clinic all specialties represented.									
21	No	—	3	Operates "Well" and "Sick" clinics. Orthopedic and dermatologic are the only special clinics.										
22	Yes	Yes	15	Co	Co	Co	Co	1	Co	0	0	0	0	1
23	Yes	Yes	6	5	2	0	0	0	Yes	0	0	0	0	0
24	—	—	—	—	—	No dispensary		—	—	—	—	—	—	—
25	No	—	8	3	3	3	3	1	0	0	0	2	Yes	0
26	Yes	Yes	6	2	2	4	5	3	1	0	1	1	0	1
27	Yes	Yes	12	Co	Co	Co	Co	Co	Co	Co	Co	Co	1	1
28	Yes	No	8	1	11	3	3	1	2	2	0	3	0	0
29	Yes	Yes	16	6	9	2	3	2	1	0	1	1	1	2
30	Yes	Yes	12	4	14	7	11	4	1	0	0	1	0	4
31	No	—	5	4	3	5	2	2	1	1	0	0	0	0
					C		C	C	C	C				
32	Yes	Yes	11	5	6	2	2	4	2	0	0	1	1	1
33	Yes	Yes	10	2	5	3	3	2	1	0	0	1	0	1
34	No	—	12	5	5	Gen. surg.	4	2	4	0	0	0	0	0
35	?	?	6	2	4	?	1	2	0	0	0	5	0	0

All the dispensaries have a regular pediatric attending staff varying in number from one to forty-four. Eighteen have an attending staff of ten or more; eleven have fifteen or more. Only six have twenty or more attending pediatricians.

Twenty-five dispensaries have regularly attending surgeons. Their number varies from one to twenty-one. In three instances surgeons are used only in a consulting capacity.

Twenty-two dispensaries have regular attending otolaryngologists. Five dispensaries have otolaryngologists only as consultants.

Twenty dispensaries have regular attending orthopedists. Five dispensaries have orthopedic surgeons only as consultants.

Twenty dispensaries have regular attending opthalmologists. Five dispensaries have opthalmologists only as consultants.

Twenty-one dispensaries have regular attending neurologists, and five have neurologists only as consultants.

Eleven dispensaries have regular attending psychologists. Four have psychologists only as consultants.

Eight dispensaries have regular attending psychiatrists. Three dispensaries have consulting psychiatrists, and one dispensary combines the two.

Twenty dispensaries have regular attending dentists. The remainder refer their dental work elsewhere. Eight dispensaries have regular attending oral hygienists. The remainder refer this work elsewhere. Eighteen dispensaries have regular attending allergists.

Apparently a majority of the dispensaries have well-organized special clinics. This fact is best illustrated by Tables III and IV.

The previous report dealing with the hospital bacteriologic, chemical and pathologic laboratories included in part the data upon the dispensary laboratories.

A summary of the important facts concerning these facilities in the dispensary reveals that fifteen hospitals have special clinical laboratories for the dispensary. These laboratories, except two, are all considered adequate for their respective dispensaries.

Twenty-seven dispensaries have the hospital laboratories available for their use. Only two dispensaries report inadequate serologic or bacteriologic laboratory facilities.

Twenty-four dispensaries report provision for simple photography. Two dispensaries report having inadequate x-ray facilities. Twenty-three dispensaries use the hospital x-ray equipment. Five dispensaries have separate x-ray equipment.

Four dispensaries have no provision for physiotherapy. Eleven dispensaries do not have an attending dietitian. All dispensaries report adequate nursing service. Only two dispensaries have no social service.

Conclusions

A well-organized, efficient and well-attended out-patient dispensary is a valuable asset to a hospital. This is particularly true if the hospital is used as a teaching hospital. The most effective dispensary service should be near to and run in close cooperation with the hospital. Nearly all of the dispensaries included in this report meet this requirement.

An accurate impression of the physical layout and equipment as depicted by the questionnaires is difficult. One receives the impression that the majority of these units have in normal times adequate space and equipment to carry on efficient work. During recent years many have been taxed beyond their capacity.

The large attendances for the most part are found in the larger cities. Only one dispensary reporting an attendance of thirty thousand a year or more is found west of the Mississippi River, and of something over one million attendance in the combined dispensaries during the past year (1932-1933) more than 80 per

TABLE III

HOSPITAL	SPECIAL CLINICS	MEDICAL CLINIC GENERAL	MEDICAL CLINIC SPECIAL	CARDIAC	NEPHRITIC	DIABETIC	TUBERCULOSIS	VAGINITIS	ENDOCRINOLOGY	ALLERGY	SURGICAL
1	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
3	—	—	—	—	No dispensary		—	—	—	—	—
4	Yes	Yes	Yes	Yes	GM*	GM	GM	Yes	No	No	Yes
5	Yes	Yes	Yes	No special clinics are conducted but consultation is readily available for all specialties.							
6	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
7	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	WA†
8	—	—	—	—	No dispensary		—	—	—	—	—
9	Yes	Yes	Yes	Yes	GM	GM	GM	?	?	GM	Yes
10	Yes	Yes	Diab.	No	No	No	No	No	No	No	No
11	No	Yes	No	With exception of orthopedic and dental services patients are referred to other clinics for attention in various specialties.							
13	Yes	Yes	No	—	Referred to special clinics					—	—
14	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
15	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
16	Yes	Yes	Yes	Yes	Yes	Yes	No WA	No WA	No WA	Yes WA	No WA
17	Yes	Yes	Yes	No	No	No	Yes	No	No	No	Yes
18	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes
19	Yes	Yes	Yes	Yes	Yes	Yes	GM	Yes	No	Yes	Yes
20	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
21	No	Yes	No	Dermatologic and orthopedic are only special clinics. Consultation available to general medical clinic in any specialties.							
22	No	Yes	No	GM	GM	GM	GM	GM	GM	GM	GM
23	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes
24	—	—	—	—	No dispensary		—	—	—	—	—
25	Yes	Yes	Yes	No	No	No	No	Yes	No	No	Yes
26	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	Yes
27	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No
28											
29	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
30	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes
31	Yes	Yes	Yes	Yes	No	GM	No	No	Yes	No	Yes
32	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
33	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes
34	Yes	Yes	Yes	Yes	Combined		Yes	Yes	Com. Neph.	No	Yes
35	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes

*GM—General Medical Clinic.
†WA—With Adult Clinic.

cent occurred east of the Mississippi River. The figures, of course, for the most part reflect the relative densities of population of the two areas.

In general, the attending staffs of the dispensaries include all usual specialties and in most instances these men serve in both the hospital and the dispensary. We are pleased to report that teaching is carried on in twenty-one dispensaries.

TABLE IV

HOSPITAL	OTO-LARYNGOLOGY	ORTHOPEDIC	POSTURE	EYE	DERMATOLOGY	SYPHILIS	NEUROLOGY	BEHAVIOR	PSYCHIATRIC	SPEECH DEFECTS	DENTAL	ORAL HYGIENE	HEART CLINIC	OTHER SPECIAL CLINICS
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes
2	Yes	Yes	Yes	Yes	Combined		Yes	Child Psy.		No	Yes	Yes	Yes	No
3	—	—	—	—	—	No dispensary			—	—	—	—	—	—
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Combined		No	Yes	No	Yes	No
5	No special clinics are conducted but consultation is readily available for all specialties.													
6	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
7	WA	WA	No	WA	WA	No	WA	No	WA	No	WA	No	No	No
8	—	—	—	—	—	No dispensary			—	—	—	—	—	—
9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	?	?	Yes	No
10	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No
11	With exception of orthopedic and dental services patients are referred to other clinics for attention in various specialties.													
13	—	—	—	—	—	Referred to special clinics					—	—	—	—
14	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes
15	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No
16	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No
	WA	WA	WA	WA	WA	WA	WA	WA	WA	WA	WA	WA		
17	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No
18	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No
19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Combined		No	Combined		Yes	Yes
20	GC	GC	Yes	GC	GC	GC	GC	Yes	GC	No	Yes	Yes	Yes	Yes
21	Dermatologic and orthopedic are only special clinics. Consultation available to general medical clinic in any specialties.													
22	GM	GM	GM	GM	GM	GM	GM	GM	GM	GM	GM	GM	GM	GM
23	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No
24	—	—	—	—	—	No dispensary			—	—	—	—	—	—
25	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes
26	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes
27	No	No	No	No	Yes	No	Yes	No	No	No	Yes	Yes	No	Yes
28	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
29	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
30	No	Yes	No	No	Combined		Yes	No	No	Yes	Yes	No	Yes	No
31	Yes	Yes	No	No	Yes	No	No	No	No	No	No	No	No	Yes
32	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes
33	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	No
34	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
35	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	No

Without a doubt dispensary experience is a valuable part of medical training and most of the children's hospitals appear to recognize their responsibility in this respect.

Many dispensaries maintain well-organized special clinics in which valuable research work as well as teaching is being done.

Data concerning laboratories, x-ray, physiotherapy, nursing, etc., all of which have been dealt with in part in previous reports, indicate that the majority of dispensaries are well equipped for effective work in these departments. Possibly more than will admit need improvement in some departments. There are at least a small number who frankly admit a weakness in one or several departments. These, it can be expected, will probably be the first to correct their faults.

Academy News

A special committee on the revision of the *Pharmacopoeia of the United States* has been appointed to represent the American Academy of Pediatrics. Its membership consists of:

Chairman, Dr. Isaac A. Abt, Chicago
Dr. William N. Bradley, Philadelphia
Dr. John Ruhräh, Baltimore
Dr. Louis W. Sauer, Evanston, Ill.

Regional meetings announced for the fall of 1934 are as follows:

Region I, New York City, October 19 and 20, with headquarters at the Ambassador Hotel, Fifty-First Street and Park Avenue.

The Region I meeting will be conducted jointly by the Academy, the New England Pediatric Society, the Philadelphia Pediatric Society, and the Section of Pediatrics of the Academy of Medicine in New York City. The meeting will be chiefly clinical in nature.

Region II, San Antonio, Texas, November 13, in conjunction with the Pediatric Section of the Southern Medical Association.

Region III, Minneapolis and Rochester, Minn., October 5 and 6.

Region III will hold its first clinical meeting in Rochester and Minneapolis, Minn., on October 4, 5, and 6. On October 4 the morning and afternoon sessions will be held in Plummer Hall at the Mayo Clinic. At one o'clock there will be a viewing of the Clinic and at 5:30 of the Experimental Institute of Medicine and St. Mary's Hospital. In the evening there will be an informal dinner at which Mr. Perry Smith, headmaster of the Winnetka Country Day School, has been asked to talk on "Advances in Education." A special train will take the members to Minneapolis that night arriving there early Friday morning. On Friday the clinical sessions in the morning and afternoon will be held in the Anatomical Amphitheater of the University of Minnesota. A dinner and informal get-together will be held at the Minneapolis Club Friday evening. The following morning there will be held the annual meeting of Region III with reports from all of the state chairmen followed by a symposium on "The Indications and Technic of Serum Administration."

The Nicollet Hotel will be the headquarters in Minneapolis, and the Kahler Hotel will be the headquarters in Rochester.

The final program will be sent to the members of Region III about September 15.

Dr. E. R. McCluskey of Pittsburgh has accepted the cochairmanship for Pennsylvania.

Dr. Clifford Sweet of Oakland California has accepted the cochairmanship with Dr. Stork for California.

Dr. Vivian Tappan of Tucson, Arizona, has accepted the state chairmanship for Arizona.

Dr. Warren Quillian of Coral Gables, Florida, has accepted the appointment as state chairman for Florida.

Book Reviews

The Life of Sir Robert Jones. FREDERICK WATSON, William Wood & Company, Baltimore, 1934, pp. 327.

While the name of Sir Robert Jones of Liverpool, who has been perhaps the most important personality in the development of modern orthopedics, will be connected in medical history chiefly with the surgery of the World War, his pioneer work and his lifelong interest in the problems of the crippled child make this biography of more than passing interest to the pediatrician. The chapter on "Baschurch" the protoype of the open-air hospital for crippled children is most interesting. The development from this of a national scheme of central hospitals and after-care clinics for crippled children was due in large part to his never-ending devotion, interest, and work. In a sense his war work was an interlude.

The first professional recognition of Sir Robert's stature as a man and his ability as a surgeon came largely from American surgeons, and he became a most important figure in developing a close relationship between English and American physicians. America owes him a great debt for his help in developing war surgery and his training of American surgeons. The author, his son-in-law and late associate, has built the biography around the personality of Sir Robert and has given us a picture of the man himself rather than a technical analysis of his work. Sir Robert Jones was one of the important men of modern medicine despite the fact that his only laboratory was the clinic. In every sense of the word he represented the finest type of physician.

B. S. V.

The Spastic Child. MARGUERITE K. FISCHEL, The C. V. Mosby Company, St. Louis, 1934, pp. 97.

This monograph is not only of value from a medical standpoint but is an intensely interesting human document. It is a mother's story of her many years of work with her child with Little's disease. By never-ending patience and perseverance and by the use of methods of her own device, she accomplished astounding and unusual muscle control. The methods she used are described in detail. The book would be of value not only to any one facing the problems of Little's disease, but to any parent with a handicapped child, as it shows what may be accomplished under the most discouraging conditions. It is an intimate personal book of an unusual nature.

Comments

FOR some time a committee of the Philadelphia Pediatric Society has been studying the question of pediatric therapeutics in relation to the Pharmacopoeia of the United States and The National Formulary. After communicating with and obtaining an opinion from many pediatricians and pediatric societies, a resolution was prepared requesting the officers of the Pharmacopoeial and Formulary Conventions of 1930 to appoint a representative group of pediatricians to suggest and advise regarding remedial agents to be deleted, retained and added to the Pharmacopoeia and Formulary. It further makes application for a permanent seat as delegates to the convention in 1940. This resolution was adopted at the May meeting of the American Pediatric Society, the June meetings of the American Academy of Pediatrics and the Section on Pediatrics of the A. M. A., and by the House of Delegates of the A. M. A.

The motive back of the resolution is an attempt to reestablish the use of drugs and remedial agents prescribed by physicians in place of the use of proprietary products. A further purpose is to put dosage for children on a sound and satisfactory basis. If such a committee is appointed, which undoubtedly will be the case, on the basis of such an overwhelming demand on the part of pediatricians and general practitioners, it is planned to have a committee make a thorough study of the drugs considered useful and important in the practice of pediatrics, by contacting pediatricians throughout the country. Such efforts should help overcome therapeutic nihilism and create a better knowledge and understanding of useful drugs throughout the medical profession.

The Philadelphia Pediatric Society, one of the oldest, largest, and most active local organizations in our field, has initiated an important movement, and we are indebted to it for its willingness to assume leadership in the long, tedious and time-consuming task which it has undertaken. The Pharmacopoeia and Formulary are revised every ten years, and as the next revision will be in 1940, there is ample time for a sound revision of pediatric therapeutics.